

08/468145

Trying 3106016892...Open

Welcome to STN International! Enter x:x  
LOGINID:sssptal813nmx  
PASSWORD:  
TERMINAL (ENTER 1, 2, 3, OR ?):2

\* \* \* \* \* Welcome to STN International \* \* \* \* \*

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America  
NEWS 2 Dec 17 The CA Lexicon available in the CAPLUS and CA files  
NEWS 3 Feb 06 Engineering Information Encompass files have new names  
NEWS 4 Feb 16 TOXLINE no longer being updated  
NEWS 5 Apr 23 Search Derwent WPINDEX by chemical structure  
NEWS 6 Apr 23 PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA  
NEWS 7 May 07 DGENE Reload  
NEWS 8 Jun 20 Published patent applications (A1) are now in USPATFULL  
NEWS 9 JUL 13 New SDI alert frequency now available in Derwent's  
DWPI and DPCI

NEWS EXPRESS July 11 CURRENT WINDOWS VERSION IS V6.0b,  
CURRENT MACINTOSH VERSION IS V5.0C (ENG) AND V5.0JB (JP),  
AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2001  
NEWS HOURS STN Operating Hours Plus Help Desk Availability  
NEWS INTER General Internet Information  
NEWS LOGIN Welcome Banner and News Items  
NEWS PHONE Direct Dial and Telecommunication Network Access to STN  
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that  
specific topic.

All use of STN is subject to the provisions of the STN Customer  
agreement. Please note that this agreement limits use to scientific  
research. Use for software development or design or implementation  
of commercial gateways or other similar uses is prohibited and may  
result in loss of user privileges and other penalties.

\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 12:32:54 ON 17 JUL 2001

=> file embase medline biosis uspatfull japio wpids caplus agricola lifesci  
biotechds jicst-eplus

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.30	0.30

FULL ESTIMATED COST

FILE 'EMBASE' ENTERED AT 12:33:40 ON 17 JUL 2001  
COPYRIGHT (C) 2001 Elsevier Science B.V. All rights reserved.

FILE 'MEDLINE' ENTERED AT 12:33:40 ON 17 JUL 2001

FILE 'BIOSIS' ENTERED AT 12:33:40 ON 17 JUL 2001

COPYRIGHT (C) 2001 BIOSIS(R)

FILE 'USPATFULL' ENTERED AT 12:33:40 ON 17 JUL 2001  
CA INDEXING COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'JAPIO' ENTERED AT 12:33:40 ON 17 JUL 2001  
COPYRIGHT (C) 2001 Japanese Patent Office (JPO)

FILE 'WPIDS' ENTERED AT 12:33:40 ON 17 JUL 2001  
COPYRIGHT (C) 2001 DERWENT INFORMATION LTD

FILE 'CAPLUS' ENTERED AT 12:33:40 ON 17 JUL 2001  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2001 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'AGRICOLA' ENTERED AT 12:33:40 ON 17 JUL 2001

FILE 'LIFESCI' ENTERED AT 12:33:40 ON 17 JUL 2001  
COPYRIGHT (C) 2001 Cambridge Scientific Abstracts (CSA)

FILE 'BIOTECHDS' ENTERED AT 12:33:40 ON 17 JUL 2001  
COPYRIGHT (C) 2001 DERWENT INFORMATION LTD

FILE 'JICST-EPLUS' ENTERED AT 12:33:40 ON 17 JUL 2001  
COPYRIGHT (C) 2001 Japan Science and Technology Corporation (JST)

=> e engel jurgen/au

E1	1	ENGEL JULIE S/AU
E2	2	ENGEL JUNE/AU
E3	208 -->	ENGEL JURGEN/AU
E4	1	ENGEL JURGN/AU
E5	18	ENGEL JUTTA/AU
E6	442	ENGEL K/AU
E7	11	ENGEL K A/AU
E8	21	ENGEL K C/AU
E9	6	ENGEL K E/AU
E10	2	ENGEL K G/AU
E11	108	ENGEL K H/AU
E12	8	ENGEL K J/AU

=> s e3-e4

L1 209 ("ENGEL JURGEN"/AU OR "ENGEL JURGN"/AU)

=> e wichert burkhard/au

E1	1	WICHERT BOB/AU
E2	1	WICHERT BODO/AU
E3	11 -->	WICHERT BURKHARD/AU
E4	1	WICHERT BURKHARD V/AU
E5	5	WICHERT C/AU
E6	9	WICHERT D/AU
E7	1	WICHERT D M/AU
E8	6	WICHERT E/AU
E9	2	WICHERT E V O N/AU
E10	8	WICHERT EDWARD/AU
E11	5	WICHERT F/AU
E12	2	WICHERT FRIEDEL/AU

=> s e3-e4

L2 12 ("WICHERT BURKHARD"/AU OR "WICHERT BURKHARD V"/AU)

=> e sauerbiar deiter/au

E1	150	SAUERBERG PER/AU
E2	1	SAUERBERG S K/AU
E3	0 -->	SAUERBIAR DEITER/AU
E4	1	SAUERBIE W/AU
E5	2	SAUERBIE WALTER/AU
E6	4	SAUERBIER A/AU
E7	4	SAUERBIER ARNIM/AU
E8	1	SAUERBIER B/AU
E9	1	SAUERBIER C/AU
E10	3	SAUERBIER C E/AU
E11	7	SAUERBIER CHARLES E/AU
E12	2	SAUERBIER CHRISTIANE/AU

=> e sauerbier deiter/au

E1	2	SAUERBIER CHRISTIANE/AU
E2	14	SAUERBIER D/AU
E3	0 -->	SAUERBIER DEITER/AU
E4	1	SAUERBIER DIESTER/AU
E5	27	SAUERBIER DIETER/AU
E6	1	SAUERBIER E/AU
E7	1	SAUERBIER F/AU
E8	3	SAUERBIER G A/AU
E9	18	SAUERBIER H/AU
E10	4	SAUERBIER HEINZ/AU
E11	1	SAUERBIER HERBERT/AU
E12	72	SAUERBIER I/AU

=> s e2-e5

L3 42 ("SAUERBIER D"/AU OR "SAUERBIER DEITER"/AU OR "SAUERBIER  
DIESTER  
"/AU OR "SAUERBIER DIETER"/AU)

=> e reissmann thomas/au

E1	2	REISSMANN T L/AU
E2	8	REISSMANN TH/AU
E3	38 -->	REISSMANN THOMAS/AU
E4	6	REISSMANN THOMAS L/AU
E5	7	REISSMANN U/AU
E6	2	REISSMANN ULRICH/AU
E7	9	REISSMANN ULRIKE/AU
E8	2	REISSMANN W/AU
E9	1	REISSMANN WALTER/AU
E10	12	REISSMANN Z/AU
E11	2	REISSMUELL A/AU
E12	1	REISSMUELL J/AU

=> s e1-e4

L4 54 ("REISSMANN T L"/AU OR "REISSMANN TH"/AU OR "REISSMANN  
THOMAS"/A  
. U OR "REISSMANN THOMAS L"/AU)

=> s 11-14

L5 284 (L1 OR L2 OR L3 OR L4)

=> s 15 and cetorelix

L6 52 L5 AND CETRORELIX

=> dup rem 16

PROCESSING COMPLETED FOR L6

L7 38 DUP REM L6 (14 DUPLICATES REMOVED)

=> s 17 and (infertil? or fertili?)

UNMATCHED LEFT PARENTHESIS 'AND (INFERTIL?'

The number of right parentheses in a query must be equal to the number of left parentheses.

=> s 17 and (infertil? or fertili?)

L8 11 L7 AND (INFERTIL? OR FERTILI?)

=> d bib ab 1-11

L8 ANSWER 1 OF 11 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 95280014 EMBASE

DN 1995280014

TI Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of **infertility**: An overview.

AU **Reissmann Th.**; Felberbaum R.; Diedrich K.; Engel J.;

Comaru-Schally A.M.; Schally A.V.

CS ASTA Medica AG, Frankfurt-M, Germany

SO Human Reproduction, (1995) 10/8 (1974-1981).

ISSN: 0268-1161 CODEN: HUREEE

CY United Kingdom

DT Journal; Article

FS 003 Endocrinology

010 Obstetrics and Gynecology

037 Drug Literature Index

038 Adverse Reactions Titles

LA English

SL English

AB Luteinizing hormone-releasing hormone (LHRH) plays a crucial role in controlling the ovarian cycle in women. By modification of the molecular structure of this decapeptide, analogues were synthesized with agonistic or antagonistic effects on the gonadotrophic cells of the anterior pituitary gland. The agonists, after an initial stimulatory effect

('flare up'), lead to desensitization of the gonadotrophic cells and a reduction in the number of LHRH receptors on the cell membrane ('down-regulation'), while the antagonists produce an immediate effect by competitive blockade of the LHRH receptors. After administration of LHRH antagonists, the

serum

levels of FSH and LH decrease within hours. Nevertheless, the adenohypophysis maintains its responsiveness to an LHRH stimulus ('pituitary response') after pretreatment with an antagonist. This different pharmacological mechanism of LHRH antagonists makes possible

new

approaches to ovarian stimulation and to the therapy of sex steroid dependent diseases. The premature LH surge, the main cause of

cancellation

during induction of superovulation in assisted reproduction technology (ART) programmes, can be abolished by short term application of an LHRH antagonist associated with a reduced human menopausal gonadotrophin (HMG) requirement for ovarian stimulation. A future approach to ART might be based on the combination of pretreatment with an LHRH antagonist and ovulation induction by native LHRH or an agonist. The severe side effects encountered with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, especially **Cetrorelix** which is presently used

clinically in controlled phase II clinical studies.

- L8 ANSWER 2 OF 11 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.  
AN 94179320 EMBASE  
DN 1994179320  
TI Introduction of LHRH-antagonists into the treatment of gynaecological disorders.  
AU **Reissmann Th.**; Diedrich K.; Comaru-Schally A.M.; Schally A.V.  
CS Clinic Obstetrics and Gynaecology, University of Lubeck, Lubeck, Germany  
SO Human Reproduction, (1994) 9/5 (767-769).  
ISSN: 0268-1161 CODEN: HUREEE  
CY United Kingdom  
DT Journal; (Short Survey)  
FS 010 Obstetrics and Gynecology  
021 Developmental Biology and Teratology  
030 Pharmacology  
037 Drug Literature Index  
LA English
- L8 ANSWER 3 OF 11 BIOSIS COPYRIGHT 2001 BIOSIS  
AN 1998:409001 BIOSIS  
DN PREV199800409001  
TI The luteal phase of nonsupplemented cycles after ovarian superovulation with human menopausal gonadotropin and the gonadotropin-releasing hormone antagonist **cetrorelix**.  
AU Albano, Carola (1); Grimbizis, Grigoris; Smits, Johan; Riethmueller-Winzen, Hilde; **Reissmann, Thomas**; Van Steirteghem, Andre; Devroey, Paul  
CS (1) Centre Reproductive Med., Brussels Free Univ., Laarbeeklaan 101, 1090 Brussels Belgium  
SO Fertility and Sterility, (Aug., 1998) Vol. 70, No. 2, pp. 357-359.  
ISSN: 0015-0282.  
DT Article  
LA English  
AB Objective: To analyze the luteal phase of six patients undergoing controlled ovarian hyperstimulation (COH) with hMG and a new GnRH antagonist, **Cetrorelix**, without receiving luteal phase supplementation. Design: Phase II study involving the first six patients who did not receive luteal phase support. Setting: Tertiary referral center. Patient(s): Six healthy women undergoing COH for assisted reproductive techniques. Intervention(s): Oocyte retrieval was performed 36 hours after hCG administration, followed by embryo transfer 2 days later. No luteal phase supplementation was given. Main Outcome Measure(s): Serum E2, progesterone, LH, and FSH concentrations were measured. Result(s): The length of the luteal phase was  $\leq$  12 days in three of the six patients. One of the patients in whom the luteal phase was >12 days had a low serum progesterone concentration (2.9 ng/mL) on day 10. Serum LH concentrations decreased after the preovulatory hCG injection in all patients. However, a progressive increase in LH was observed after day 7, reaching normal values. Conclusion(s): Corpus luteum function seems to be impaired in cycles that are stimulated with hMG and the GnRH antagonist **Cetrorelix**.
- L8 ANSWER 4 OF 11 BIOSIS COPYRIGHT 2001 BIOSIS  
AN 1995:415178 BIOSIS  
DN PREV199598429478  
TI Preserved pituitary response under ovarian stimulation with hMG and GnRH antagonists (**Cetrorelix**) in women with tubal infertility  
AU Felberbaum, Ricardo E. (1); **Reissmann, Thomas**; Kuepker, Wolfgang; Bauer, Otmar; Al Hasani, Safaa; Diedrich, Christa; Diedrich, Klaus

CS (1) Dep. of Obstetrics and Gynecology, Medical Univ. of Luebeck, Luebeck  
Germany

SO European Journal of Obstetrics & Gynecology and Reproductive Biology,  
(1995) Vol. 61, No. 2, pp. 151-155.  
ISSN: 0301-2115.

DT Article

LA English

AB Objective: To examine the pituitary response in patients undergoing  
short-term application of the GnRH antagonist **Cetrorelix** in the  
mid-cycle phase for hypophysial suppression of premature LH surges within  
an IVF-program. Design: Twenty patients suffering from primary or  
secondary tubal **infertility** were stimulated with hMG from cycle  
day 2. From day 7 till ovulation induction **Cetrorelix** was  
administered in two different dose regimens (15 patients 3 mg s.c. daily;  
5 patients 1 mg s.c. daily). Three hours before ovulation induction a  
GnRH test was performed using 25 mu-g of native GnRH and the pituitary  
response examined by measurement of the serum LH concentration after 30 min.  
Results: Premature LH surges could be avoided in the 3-mg group and in  
the 1-mg group, respectively. Due to this, none of the cycles had to be  
cancelled. Oestradiol profiles and ultrasound demonstrated a satisfactory  
follicular maturation. All patients showed pronounced suppression of the  
serum LH levels before ovulation induction. The mean increase of serum LH  
due to the performed GnRH test was 10 mIU/ml for the 3-mg group, while  
the average maximum in the 1-mg group was about 32.5 mIU/ml. Conclusions: The  
pituitary response is preserved by the treatment with the GnRH antagonist  
**Cetrorelix**. The extent of suppression of the adenohypophysis, as  
expressed by the different reactions on GnRH test, can be modulated by  
the dosage administered. This should allow ovulation induction by GnRH or one  
of its agonists instead of hCG, which could be beneficial in patients at  
high risk of Ovarian Hyperstimulation Syndrome (OHSS) and those suffering  
from Polycystic Ovary Disease (PCOD).

L8 ANSWER 5 OF 11 USPATFULL

AN 97:78416 USPATFULL

TI Products for administering an initial high dose of **Cetrorelix**  
and producing a combination package for use when treating diseases

IN **Engel, Jurgen**, Alzenau, Germany, Federal Republic of  
Hilgard, Peter, Frankfurt, Germany, Federal Republic of  
**Reissmann, Thomas**, Frankfurt, Germany, Federal Republic of

PA ASTA Medica Aktiengesellschaft, Dresden, Germany, Federal Republic of  
(non-U.S. corporation)

PI US 5663145 19970902

AI US 1994-354838 19941208 (8)

PRAI DE 1993-4342091 19931209

DT Utility

FS Granted

EXNAM Primary Examiner: Russel, Jeffrey E.

LREP Cushman Darby & Cushman IP Group of Pillsbury Madison & Sutro LLP

CLMN Number of Claims: 25

ECL Exemplary Claim: 7

DRWN No Drawings

LN.CNT 227

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB For application during the treatment of benign and malign tumour  
diseases, the product according to the invention containing the initial  
dose of **Cetrorelix** acetate and one or more maintenance doses  
of **Cetrorelix** acetate, **Cetrorelix** embonate or a  
slow-release form of **Cetrorelix**, is used as a combination  
preparation for treatment to be administered at specific time  
intervals.

L8 ANSWER 6 OF 11 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
 AN 1999-542841 [46] WPIDS  
 CR 1994-265229 [33]  
 DNC C1999-158621  
 TI Treatment of female **infertility**, especially by in-vitro **fertilization**.  
 DC B04  
 IN ENGEL, J; REISSMANN, T; SAUERBIER, D; WICHERT, B  
 PA (ASTA) ASTA MEDICA AG  
 CYC 17  
 PI EP 947200 A2 19991006 (199946)\* DE 5p  
 R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE  
 ADT EP 947200 A2 Div ex EP 1994-101672 19940204, EP 1999-102340 19940204  
 FDT EP 947200 A2 Div ex EP 611572  
 PRAI DE 1993-4305225 19930219  
 AB EP 947200 A UPAB: 19991110  
 NOVELTY - Sterile freeze-dried **cetrorelix** acetate (a peptide described in EP299402) is used in the treatment of female **infertility**.  
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) use of sterile freeze-dried **cetrorelix** acetate for protecting gonads against noxious agents that damage germ cells, e.g. radiation treatment and chemotherapy; (2) a composition comprising sterile freeze-dried **cetrorelix** acetate and optionally excipients for use in the treatment of female **infertility**; (3) a composition comprising sterile freeze-dried **cetrorelix** acetate and optionally excipients for protecting gonads against noxious agents that damage germ cells, e.g. radiation treatment and chemotherapy with cytostatic agents.  
 ACTIVITY - None given.  
 MECHANISM OF ACTION - Luteinizing hormone-releasing hormone (LHRH) antagonist.  
 USE - In an in-vitro **fertilization** procedure in which **cetrorelix** is administered to control the time of ovulation during an ovary stimulation treatment by preventing a pre-ovulation increase in luteinizing hormone (LH) levels, whereupon exogenous gonadotropin is administered to induce ovulation after follicle maturation.  
 Dwg.0/0

L8 ANSWER 7 OF 11 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
 AN 1994-265229 [33] WPIDS  
 DNC C1994-121294  
 TI Freeze-dried peptide compsns. - prepd. by freeze drying soln. of peptide in aq. acetic acid.  
 DC B04  
 IN ENGEL, J; REISSMANN, T; SAUERBIER, D; WICHERT, B; BURKHARD, W; JUERGEN, E  
 PA (ASTA) ASTA MEDICA AG  
 CYC 32  
 PI EP 611572 A2 19940824 (199433)\* DE 5p  
 R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE  
 DE 4305225 A1 19940825 (199433) 5p  
 AU 9455235 A 19940825 (199436)  
 NO 9400564 A 19940822 (199436)  
 CA 2115943 A 19940820 (199439)  
 CZ 9400312 A3 19940914 (199439)  
 BR 9400617 A 19940927 (199440)  
 SK 9400195 A3 19940907 (199440)  
 FI 9400779 A 19940820 (199441)  
 JP 06271476 A 19940927 (199443) 5p  
 ZA 9401136 A 19941026 (199444) 12p  
 HU 67117 T 19950228 (199514)  
 EP 611572 A3 19950111 (199538)

AU 671881 B 19960912 (199644)  
 CN 1112019 A 19951122 (199737)  
 SG 46632 A1 19980220 (199822)  
 BR 1101004 A3 19980512 (199828)  
 CZ 284314 B6 19981014 (199847)  
 NZ 314707 A 19990225 (199914)  
 CZ 285768 B6 19991117 (200002)  
 EP 611572 B1 20000607 (200032) DE  
 R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE  
 DE 59409389 G 20000713 (200037)  
 HU 218281 B 20000728 (200045)  
 RU 2145234 C1 20000210 (200048)  
 ES 2148247 T3 20001016 (200058)  
 TW 387812 A 20000421 (200061)  
 ADT. EP 611572 A2 EP 1994-101672 19940204; DE 4305225 A1 DE 1993-4305225  
 19930219; AU 9455235 A AU 1994-55235 19940217; NO 9400564 A NO 1994-564  
 19940218; CA 2115943 A CA 1994-2115943 19940218; CZ 9400312 A3 CZ  
 1994-312  
 19940214; BR 9400617 A BR 1994-617 19940218; SK 9400195 A3 SK 1994-195  
 19940218; FI 9400779 A FI 1994-779 19940218; JP 06271476 A JP 1994-20532  
 19940217; ZA 9401136 A ZA 1994-1136 19940218; HU 67117 T HU 1994-481  
 19940218; EP 611572 A3 EP 1994-101672 19940204; AU 671881 B AU 1994-55235  
 19940217; CN 1112019 A CN 1994-101378 19940218; SG 46632 A1 SG 1996-6874  
 19940204; BR 1101004 A3 BR 1997-1101004 19970514; CZ 284314 B6 CZ  
 1994-312  
 19940214; NZ 314707 A Div ex NZ 1994-250906 19940217, NZ 1994-314707  
 19940217; CZ 285768 B6 CZ 1998-974 19940214; EP 611572 B1 EP 1994-101672  
 19940204, Related to EP 1999-102340 19940204; DE 59409389 G DE  
 1994-509389  
 19940204, EP 1994-101672 19940204; HU 218281 B HU 1994-481 19940218; RU  
 2145234 C1 RU 1994-5001 19940218; ES 2148247 T3 EP 1994-101672 19940204;  
 TW 387812 A TW 1994-100769 19940131  
 FDT AU 671881 B Previous Publ. AU 9455235; CZ 284314 B6 Previous Publ. CZ  
 9400312; NZ 314707 A Div ex NZ 250906; CZ 285768 B6 Previous Publ. CZ  
 9800974; EP 611572 B1 Related to EP 947200; DE 59409389 G Based on EP  
 611572; HU 218281 B Previous Publ. HU 67117; ES 2148247 T3 Based on EP  
 611572  
 PRAI DE 1993-4305225 19930219  
 AB EP 611572 A UPAB: 19991110  
 Freeze-dried compsns. comprising a peptide of 3-15 amino acid units and  
 opt. one or more matrix materials are characterised in that 1 pt. wt. of  
 the peptide is dissolved in 100-10,000 pts. wt. of acetic acid and then  
 transferred to water and the resulting soln. is freeze dried.  
 USE/ADVANTAGE - The compsns. esp. contain **cetrorelix** (EP  
 299402), which is used in the treatment of female **infertility**  
 (for controlling ovulation prior to isolating egg cells for in-vitro  
**fertilisation**) and for gonad protection in male patients (e.g.  
 undergoing radio- or chemotherapy). The aq. acetic acid soln. can be  
 sterilised by filtration without gelation or hydrolysis of the peptide.  
 Dwg.0/0

L8 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2001 ACS

AN 2000:725497 CAPLUS

DN 133:261948

TI Method for a programmed controlled ovarian stimulation protocol

IN **Engel, Jürgen**; Riethmuller-winzen, Hilde

PA Asta Medica A.-G., Germany

SO PCT Int. Appl., 17 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000059542	A1	20001012	WO 2000-EP2466	20000321



W: AU, BG, BR, BY, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI US 1999-127241 P 19990331  
US 1999-131632 P 19990428

AB A method of therapeutic management of **infertility** by programming of controlled ovarian stimulation (COS) and assisted reproductive procedures (ART) the improvement consisting of (a) suppression of premature ovulation with an LHRH-antagonist in controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) with multiple follicle and oocyte development; (b) programming the start of controlled ovarian stimulation (COS) by the administration of progestogen only - or alternatively combined oral contraceptive preps.; (c) exogenous stimulation of the ovarian follicle growth; (d) ovulation induction with HCG, native LHRH, LHRH-agonists or recombinant LH; (e) application of assisted reprod. techniques, esp. of IVF, ICSI, GIFT, ZIFT or by intrauterine insemination by sperm injection.

RE.CNT 6

RE

- (1) Albano, C; HUMAN REPRODUCTION 1996, V11/10(2114-2118)
- (2) Asta Medica Ag; EP 0788799 A 1997 CAPLUS
- (3) Asta Medica Ag; CA 2200541 A 1998 CAPLUS
- (4) Bouchard, P; OVULATION INDUCTION: UPDATE: THE PROCEEDINGS OF THE WORLD CONGRESS ON OVULATION INDUCTION 1998, P115 CAPLUS
- (5) Felberbaum, R; IN VITRO FERT ASSISTED REPROD, PROC WORLD CONGR 1997, P397 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2001 ACS

AN 1999:708625 CAPLUS

DN 131:295922

TI Method for the treatment of **fertility** disorders using an LHRH antagonist to partially suppress endogenous gonadotropins during intrauterine insemination

IN **Engel, Jürgen; Riethmüller-Winzen, Hilde; Reissmann, Thomas**

PA Asta Medica Aktiengesellschaft, Germany

SO PCT Int. Appl., 13 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9955357	A1	19991104	WO 1999-EP2133	19990329
	W: AU, BG, BR, BY, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9937028	A1	19991116	AU 1999-37028	19990329
	BR 9909802	A	20001226	BR 1999-9802	19990329
	EP 1082129	A1	20010314	EP 1999-919152	19990329
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NO 2000005145	A	20001013	NO 2000-5145	20001013
PRAI	US 1998-82743	P	19980423		
	WO 1999-EP2133	W	19990329		

AB In the method of therapeutic management of **infertility** by intrauterine insemination the improvement consisting of (a) the dose-dependent suppression of endogenous gonadotropins, esp. LH, with a LH-RH Antagonist allowing the maintenance of physiol. estrogen levels,

(b)

exogenous stimulation of the ovarian follicle growth, (c) ovulation induction with HCG, native LHRH, LHRH-Agonists or recombinant LH, (d) intrauterine insemination by sperm injection. The LHRH Antagonists may be preferably **Cetrorelix** or Antarelix. The stimulation is performed by administration of HMG or recombinant FSH with or without recombinant LH or with antiestrogens as for example Chlomiphene as well as with the combination of antiestrogens as for example Chlomiphene with gonadotropins.

RE.CNT 5

RE

- (1) Asta Medica AG; EP 0611572 A 1994 CAPLUS
- (2) Asta Medica AG; EP 0788799 A 1997 CAPLUS
- (3) Bouchard, P; Ovul Ind Update '98, Proc World Conf, 2nd 1998, P115 CAPLUS
- (4) Crowley, W; US 5130137 A 1992 CAPLUS
- (5) Schering AG; DE 19604231 A 1997 CAPLUS

L8 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2001 ACS

AN 1999:538778 CAPLUS

DN 131:139954

TI LHRH antagonists in the treatment of **fertility** disorders

IN Bouchard, Philippe; Frydman, Rene; Diedrich, Klaus; **Engel, Jurgen**; Devroey, Paul

PA Asta Medica AG, Germany

SO Can. Pat. Appl., 15 pp.

CODEN: CPXXEB

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	CA 2200541	AA	19980722	CA 1997-2200541	19970320
PRAI	US 1997-786937		19970122		

AB A method of treating **infertility** disorders by administering an LH-RH antagonist, preferably **Cetrorelix**, in amts. to selectively suppress endogenous LH but not FSH secretion and inducing follicle growth by administration of exogenous gonadotropin. The selective suppression

of

LH allows FSH secretion to be at natural levels thereby not affecting individual estrogen development. The LH-RH antagonist can be given as a single or dual s.c. dose in the range of 1 mg to 10 mg, preferably 2 mg - 6 mg. In multiple dosing posol., LH-RH antagonist can be administered s.c. in an amt. in the range of 0.1 to 0.5 mg of LH-RH antagonist/day. LH-RH antagonist is applied starting cycle day 1 to 10, preferably on day 4 to 8, and ovulation can be induced between day 9 and 20 of the menstruation cycle by administering rec. LH, native LH-RH, LH-RH agonist or by HCG. In addn. rec. LH, native LH-RH or LH-RH agonist can be given to avoid hyperstimulation syndrome and native LH-RH or a LH-RH agonist

can

neg. be administered to avoid luteal phase stimulation by neutralizing the effects of HCG.

L8 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2001 ACS

AN 1998:672495 CAPLUS

DN 129:293891

TI Immobilized activity-stabilized LHRH antagonist complexes and their production

IN Engel, Juergen; Deger, Wolfgang; **Reissmann, Thomas**; Losse, Guenter; Naumann, Wolfgang; Murgas, Sandra

PA Asta Medica Aktiengesellschaft, Germany

SO PCT Int. Appl., 22 pp.

CODEN: PIXXD2

DT Patent

LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9842381	A1	19981001	WO 1998-EP1398	19980311
	W: AU, BR, CA, CN, CZ, HU, IL, JP, MX, NO, NZ, PL, RU, SK, TR, UA				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,				
SE	DE 19712718	A1	19981001	DE 1997-19712718	19970326
	DE 19712718	C2	19990923		
	AU 9869207	A1	19981020	AU 1998-69207	19980311
	BR 9807887	A	20000222	BR 1998-7887	19980311
	EP 981377	A1	20000301	EP 1998-914877	19980311
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 6022860	A	20000208	US 1998-48244	19980326
	NO 9904665	A	19990924	NO 1999-4665	19990924
	US 6054555	A	20000425	US 1999-422990	19991022
PRAI	DE 1997-19712718		19970326		
	WO 1998-EP1398		19980311		
	US 1998-48244		19980326		

AB LHRH antagonists, esp. **cetrorelix**, are complexed with suitable biophilic carriers to enable sustained, targeted release of the active substance over a period of several weeks. The acidic polyamino acids, polyaspartic and polyglutamic acids, are selected for complexation with **cetrorelix**. The **cetrorelix**/polyamino acid complexes are produced from aq. solns. by combining the solns. and pptg. the complexes which are subsequently centrifuged off and vacuum dried over P205, preferably by lyophilization. These acidic polyamino acids display good sustained-release properties in a static liberation system depending on the hydrophobicity and molar mass of the polyamino acids. Animal testing demonstrated the efficacy of the **cetrorelix**/polyamino acid complexes as a depot system. By complexation of **cetrorelix** with polyamino acids, testosterone suppression can be achieved in male rats over a period of 600 h. Active substance release can thus be controlled according to polymer type and molar mass.

=> s l6 and (infertil? or fertil?)

L9 17 L6 AND (INFERTIL? OR FERTIL?)

=> dup rem l9

PROCESSING COMPLETED FOR L9

L10 14 DUP REM L9 (3 DUPLICATES REMOVED)

=> s l10 and gonadotrophin?

L11 1 L10 AND GONADOTROPHIN?

=> d bib ab

L11 ANSWER 1 OF 1 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 95280014 EMBASE

DN 1995280014

TI Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of **infertility**: An overview.

AU **Reissmann Th.**; Felberbaum R.; Diedrich K.; Engel J.;

Comaru-Schally A.M.; Schally A.V.

CS ASTA Medica AG, Frankfurt-M, Germany

SO Human Reproduction, (1995) 10/8 (1974-1981).

ISSN: 0268-1161 CODEN: HUREEE

CY United Kingdom

DT Journal; Article  
 FS 003 Endocrinology  
 010 Obstetrics and Gynecology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 LA English  
 SL English  
 AB Luteinizing hormone-releasing hormone (LHRH) plays a crucial role in controlling the ovarian cycle in women. By modification of the molecular structure of this decapeptide, analogues were synthesized with agonistic or antagonistic effects on the gonadotrophic cells of the anterior pituitary gland. The agonists, after an initial stimulatory effect ('flare up'), lead to desensitization of the gonadotrophic cells and a reduction in the number of LHRH receptors on the cell membrane ('down-regulation'), while the antagonists produce an immediate effect by competitive blockade of the LHRH receptors. After administration of LHRH antagonists, the serum levels of FSH and LH decrease within hours. Nevertheless, the adenohipophysis maintains its responsiveness to an LHRH stimulus ('pituitary response') after pretreatment with an antagonist. This different pharmacological mechanism of LHRH antagonists makes possible new approaches to ovarian stimulation and to the therapy of sex steroid dependent diseases. The premature LH surge, the main cause of cancellation during induction of superovulation in assisted reproduction technology (ART) programmes, can be abolished by short term application of an LHRH antagonist associated with a reduced human menopausal gonadotrophin (HMG) requirement for ovarian stimulation. A future approach to ART might be based on the combination of pretreatment with an LHRH antagonist and ovulation induction by native LHRH or an agonist. The severe side effects encountered with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, especially **Cetrorelix** which is presently used clinically in controlled phase II clinical studies.

=> d 110 bib ab 1-15

L10 ANSWER 1 OF 14 USPATFULL  
 AN 2000:109312 USPATFULL  
 TI Diagnostic composition containing an LH-RH antagonist for hysteroscopy  
 IN **Engel, Jurgen**, Alzenau, Germany, Federal Republic of  
 Diedrich, Klaus, Gross-Sarau, Germany, Federal Republic of  
 Felberbaum, Ricardo, Lubeck, Germany, Federal Republic of  
 PA Asta Medica Aktiengesellschaft, Germany, Federal Republic of (non-U.S. corporation)  
 PI US 6106805 20000822  
 AI US 1997-961085 19971030 (8)  
 PRAI DE 1996-19644994 19961030  
 DT Utility  
 FS Granted  
 EXNAM Primary Examiner: Dees, Jose' G.; Assistant Examiner: Hartley, Michael G.  
 LREP Cushman Darby & Cushman  
 CLMN Number of Claims: 5  
 ECL Exemplary Claim: 1  
 DRWN 3 Drawing Figure(s); 1 Drawing Page(s)  
 LN.CNT 173  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB The invention relates to a diagnostic composition for improving the effectiveness of hysteroscopy, characterized in that it contains an LH-RH antagonist, in particular **cetrorelix**. The composition is

envisaged for use prior to hysteroscopy and/or for preparation for surgery, specifically in a single dose of between 0.1 and 2 mg/kg.

However, the composition can also be administered, for use prior to hysteroscopy and/or for preparation for surgery, in a multiple dose of between 0.01 and 0.5 mg/kg, preferably spread over 1-14 days. The composition is furthermore suitable for use in hysteroscopy in combination with the subsequent treatment of pathological conditions of the uterus such as myoma and endometrial hyperplasia.

L10 ANSWER 2 OF 14 USPATFULL

AN 2000:50805 USPATFULL

TI Process for the preparation of immobilized and activity-stabilized complexes of LHRH antagonists

IN **Engel, Jorgen**, Alzenau, Germany, Federal Republic of  
**Deger, Wolfgang**, Frankfurt, Germany, Federal Republic of  
**Reissmann, Thomas**, Frankfurt, Germany, Federal Republic of  
**Losse, Gunter**, Dresden, Germany, Federal Republic of  
**Naumann, Wolfgang**, Zug, Germany, Federal Republic of  
**Murgas, Sandra**, Dresden, Germany, Federal Republic of

PA Asta Medica Aktiengesellschaft, Dresden, Germany, Federal Republic of (non-U.S. corporation)

PI US 6054555 20000425

AI US 1999-422990 19991022 (9)

RLI Division of Ser. No. US 1998-48244, filed on 26 Mar 1998

PRAI DE 1997-19712718 19970326

DT Utility

FS Granted

EXNAM Primary Examiner: Moezie, F. T.

LREP Pillsbury Madison & Sutro LLP

CLMN Number of Claims: 4

ECL Exemplary Claim: 1

DRWN 4 Drawing Figure(s); 4 Drawing Page(s)

LN.CNT 263

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In this invention, a release-delaying system is to be developed for LHRH

antagonists, in particular for **cetrorelix**, which allows the active compound to be released in a controlled manner over several weeks

by complexation with suitable biophilic carriers. The acidic polyamino acids polyglutamic acid and polyaspartic acid were selected for complexation with **cetrorelix**. The **cetrorelix** polyamino acid complexes are prepared from aqueous solutions by combination of the solutions and precipitation of the complexes, which are subsequently centrifuged off and dried over P.sub.2 O.sub.5 in vacuo. If complexes having a defined composition are to be obtained, lyophilization proves to be a suitable method. The **cetrorelix**-carboxylic acid complexes were also prepared from the aqueous solutions. In the random liberation system, the acidic polyamino acids poly-Glu and poly-Asp showed good release-delaying properties as a function of the hydrophobicity and the molecular mass of the polyamino acid. In animal experiments, it was possible to confirm the activity of the **cetrorelix**-polyamino acid complexes as a depot system in principle. It is thus possible by complexation of **cetrorelix** with polyamino acids to achieve testosterone suppression in male rats over 600 hours. The release of active compound here can be controlled

by the nature and the molecular mass of the polymers.

L10 ANSWER 3 OF 14 USPATFULL

AN 2000:15636 USPATFULL

TI Immobilized and activity-stabilized complexes of LHRH antagonists and processes for their preparation

IN **Engel, Jorgen**, Alzenau, Germany, Federal Republic of

Deger, Wolfgang, Frankfurt, Germany, Federal Republic of  
**Reissmann, Thomas**, Frankfurt, Germany, Federal Republic of  
 Losse, Gunter, Dresden, Germany, Federal Republic of  
 Naumann, Wolfgang, Zug, Germany, Federal Republic of  
 Murgas, Sandra, Dresden, Germany, Federal Republic of  
 PA Asta Medica Aktiengesellschaft, Dresden, Germany, Federal Republic of  
 (non-U.S. corporation)  
 PI US 6022860 20000208  
 AI US 1998-48244 19980326 (9)  
 PRAI DE 1997-19712718 19970326  
 DT Utility  
 FS Granted  
 EXNAM Primary Examiner: Moezie, F. T.  
 LREP Pillsbury Madison & Sutro LLP  
 CLMN Number of Claims: 7  
 ECL Exemplary Claim: 1  
 DRWN 4 Drawing Figure(s); 4 Drawing Page(s)  
 LN.CNT 271

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In this invention, a release-delaying system is to be developed for  
 LHRH  
 antagonists, in particular for **cetrorelix**, which allows the  
 active compound to be released in a controlled manner over several  
 weeks  
 by complexation with suitable biophilic carriers.

The acidic polyamino acids polyglutamic acid and polyaspartic acid were  
 selected for complexation with **cetrorelix**. The  
**cetrorelix** polyamino acid complexes are prepared from aqueous  
 solutions by combination of the solutions and precipitation of the  
 complexes, which are subsequently centrifuged off and dried over

P.sub.2

O.sub.5 in vacuo. If complexes having a defined composition are to be  
 obtained, lyophilization proves to be a suitable method. The  
**cetrorelix**-carboxylic acid complexes were also prepared from the  
 aqueous solutions.

In the random liberation system, the acidic polyamino acids poly-Glu  
 and  
 poly-Asp showed good release-delaying properties as a function of the  
 hydrophobicity and the molecular mass of the polyamino acid.

In animal experiments, it was possible to confirm the activity of the  
**cetrorelix**-polyamino acid complexes as a depot system in  
 principle. It is thus possible by complexation of **cetrorelix**  
 with polyamino acids to achieve testosterone suppression in male rats  
 over 600 hours. The release of active compound here can be controlled  
 by  
 the nature and the molecular mass of the polymers.

L10 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2001 ACS

AN 2000:725497 CAPLUS

DN 133:261948

TI Method for a programmed controlled ovarian stimulation protocol

IN **Engel, Jorgen**; Riethmuller-winzen, Hilde

PA Asta Medica A.-G., Germany

SO PCT Int. Appl., 17 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	WO 2000059542	A1	20001012	WO 2000-EP2466	20000321
	W: AU, BG, BR, BY, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP,				

KG, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR,  
UA, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
PT, SE

PRAI US 1999-127241 P 19990331  
US 1999-131632 P 19990428

AB A method of therapeutic management of **infertility** by programming of controlled ovarian stimulation (COS) and assisted reproductive procedures (ART) the improvement consisting of (a) suppression of premature ovulation with an LHRH-antagonist in controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) with multiple follicle and oocyte development; (b) programming the start of controlled ovarian stimulation (COS) by the administration of progestogen only - or alternatively combined oral contraceptive preps.; (c) exogenous stimulation of the ovarian follicle growth; (d) ovulation induction with HCG, native LHRH, LHRH-agonists or recombinant LH; (e) application of assisted reprod. techniques, esp. of IVF, ICSI, GIFT, ZIFT or by intrauterine insemination by sperm injection.

RE.CNT 6

RE

- (1) Albano, C; HUMAN REPRODUCTION 1996, V11/10(2114-2118)
- (2) Asta Medica Ag; EP 0788799 A 1997 CAPLUS
- (3) Asta Medica Ag; CA 2200541 A 1998 CAPLUS
- (4) Bouchard, P; OVULATION INDUCTION: UPDATE: THE PROCEEDINGS OF THE WORLD CONGRESS ON OVULATION INDUCTION 1998, P115 CAPLUS
- (5) Felberbaum, R; IN VITRO FERT ASSISTED REPROD, PROC WORLD CONGR 1997, P397 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 14 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1999-542841 [46] WPIDS

CR 1994-265229 [33]

DNC C1999-158621

TI Treatment of female **infertility**, especially by in-vitro fertilization.

DC B04

IN ENGEL, J; REISSMANN, T; SAUERBIER, D; WICHERT, B

PA (ASTA) ASTA MEDICA AG

CYC 17

PI EP 947200 A2 19991006 (199946)\* DE 5p

R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

ADT EP 947200 A2 Div ex EP 1994-101672 19940204, EP 1999-102340 19940204

FDT EP 947200 A2 Div ex EP 611572

PRAI DE 1993-4305225 19930219

AB EP 947200 A UPAB: 19991110

NOVELTY - Sterile freeze-dried **cetrorelix** acetate (a peptide described in EP299402) is used in the treatment of female **infertility**.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) use of sterile freeze-dried **cetrorelix** acetate for protecting gonads against noxious agents that damage germ cells, e.g. radiation treatment and chemotherapy; (2) a composition comprising sterile

freeze-dried **cetrorelix** acetate and optionally excipients for use in the treatment of female **infertility**; (3) a composition comprising sterile freeze-dried **cetrorelix** acetate and optionally excipients for protecting gonads against noxious agents that damage germ cells, e.g. radiation treatment and chemotherapy with cytostatic agents.

ACTIVITY - None given.

MECHANISM OF ACTION - Luteinizing hormone-releasing hormone (LHRH) antagonist.

USE - In an in-vitro **fertilization** procedure in which **cetrorelix** is administered to control the time of ovulation during

an ovary stimulation treatment by preventing a pre-ovulation increase in luteinizing hormone (LH) levels, whereupon exogenous gonadotropin is administered to induce ovulation after follicle maturation.  
Dwg.0/0

L10 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2001 ACS

AN 1999:708625 CAPLUS

DN 131:295922

TI Method for the treatment of **fertility** disorders using an LHRH antagonist to partially suppress endogenous gonadotropins during intrauterine insemination

IN **Engel, Jurgen**; Riethmuller-Winzen, Hilde; **Reissmann, Thomas**

PA Asta Medica Aktiengesellschaft, Germany

SO PCT Int. Appl., 13 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	WO 9955357	A1	19991104	WO 1999-EP2133	19990329
	W: AU, BG, BR, BY, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9937028	A1	19991116	AU 1999-37028	19990329
	BR 9909802	A	20001226	BR 1999-9802	19990329
	EP 1082129	A1	20010314	EP 1999-919152	19990329
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	NO 2000005145	A	20001013	NO 2000-5145	20001013
PRAI	US 1998-82743	P	19980423		
	WO 1999-EP2133	W	19990329		

AB In the method of therapeutic management of **infertility** by intrauterine insemination the improvement consisting of (a) the dose-dependent suppression of endogenous gonadotropins, esp. LH, with a LH-RH Antagonist allowing the maintenance of physiol. estrogen levels,

(b) exogenous stimulation of the ovarian follicle growth, (c) ovulation induction with HCG, native LHRH, LHRH-Agonists or recombinant LH, (d) intrauterine insemination by sperm injection. The LHRH Antagonists may

be preferably **Cetrorelix** or Antarelix. The stimulation is performed by administration of HMG or recombinant FSH with or without recombinant LH or with antiestrogens as for example Chlomiphene as well

as with the combination of antiestrogens as for example Chlomiphene with gonadotropins.

RE.CNT 5

RE

(1) Asta Medica AG; EP 0611572 A 1994 CAPLUS

(2) Asta Medica AG; EP 0788799 A 1997 CAPLUS

(3) Bouchard, P; Ovul Ind Update '98, Proc World Conf, 2nd 1998, P115 CAPLUS

(4) Crowley, W; US 5130137 A 1992 CAPLUS

(5) Schering AG; DE 19604231 A 1997 CAPLUS

L10 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2001 ACS

AN 1998:672495 CAPLUS

DN 129:293891

TI Immobilized activity-stabilized LHRH antagonist complexes and their production

IN **Engel, Juergen**; Deger, Wolfgang; **Reissmann, Thomas**; Losse, Guenter; Naumann, Wolfgang; Murgas, Sandra



PA Asta Medica Aktiengesellschaft, Germany  
SO PCT Int. Appl., 22 pp.  
CODEN: PIXXD2  
DT Patent  
LA German  
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9842381	A1	19981001	WO 1998-EP1398	19980311
	W: AU, BR, CA, CN, CZ, HU, IL, JP, MX, NO, NZ, PL, RU, SK, TR, UA				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,				

SE

	DE 19712718	A1	19981001	DE 1997-19712718	19970326
	DE 19712718	C2	19990923		
	AU 9869207	A1	19981020	AU 1998-69207	19980311
	BR 9807887	A	20000222	BR 1998-7887	19980311
	EP 981377	A1	20000301	EP 1998-914877	19980311
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 6022860	A	20000208	US 1998-48244	19980326
	NO 9904665	A	19990924	NO 1999-4665	19990924
	US 6054555	A	20000425	US 1999-422990	19991022

PRAI DE 1997-19712718 19970326  
WO 1998-EP1398 19980311  
US 1998-48244 19980326

AB LHRH antagonists, esp. **cetrorelix**, are complexed with suitable biophilic carriers to enable sustained, targeted release of the active substance over a period of several weeks. The acidic polyamino acids, polyaspartic and polyglutamic acids, are selected for complexation with **cetrorelix**. The **cetrorelix**/polyamino acid complexes are produced from aq. solns. by combining the solns. and pptg. the complexes which are subsequently centrifuged off and vacuum dried over P205, preferably by lyophilization. These acidic polyamino acids display good sustained-release properties in a static liberation system depending on the hydrophobicity and molar mass of the polyamino acids. Animal testing demonstrated the efficacy of the **cetrorelix**/polyamino acid complexes as a depot system. By complexation of **cetrorelix** with polyamino acids, testosterone suppression can be achieved in male rats over a period of 600 h. Active substance release can thus be controlled according to polymer type and molar mass.

L10 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2001 ACS

AN 1999:538778 CAPLUS

DN 131:139954

TI LHRH antagonists in the treatment of **fertility** disorders

IN Bouchard, Philippe; Frydman, Rene; Diedrich, Klaus; Engel, Jurgen ; Devroey, Paul

PA Asta Medica AG, Germany

SO Can. Pat. Appl., 15 pp.

CODEN: CPXXEB

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CA 2200541	AA	19980722	CA 1997-2200541	19970320
PRAI	US 1997-786937		19970122		

AB A method of treating **infertility** disorders by administering an LH-RH antagonist, preferably **Cetrorelix**, in amts. to selectively suppress endogenous LH but not FSH secretion and inducing follicle growth by administration of exogenous gonadotropin. The selective suppression of

LH allows FSH secretion to be at natural levels thereby not affecting individual estrogen development. The LH-RH antagonist can be given as a single or dual s.c. dose in the range of 1 mg to 10 mg, preferably 2 mg -

6 mg. In multiple dosing posol., LH-RH antagonist can be administered s.c. in an amt. in the range of 0.1 to 0.5 mg of LH-RH antagonist/day. LH-RH antagonist is applied starting cycle day 1 to 10, preferably on day 4 to 8, and ovulation can be induced between day 9 and 20 of the menstruation cycle by administering rec. LH, native LH-RH, LH-RH agonist or by HCG. In addn. rec. LH, native LH-RH or LH-RH agonist can be given to avoid hyperstimulation syndrome and native LH-RH or a LH-RH agonist can be administered to avoid luteal phase stimulation by neutralizing the neg. effects of HCG.

L10 ANSWER 9 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1998:409001 BIOSIS

DN PREV199800409001

TI The luteal phase of nonsupplemented cycles after ovarian superovulation with human menopausal gonadotropin and the gonadotropin-releasing hormone antagonist **cetrorelix**.

AU Albano, Carola (1); Grimbizis, Grigoris; Smitz, Johan; Riethmueller-Winzen, Hilde; **Reissmann, Thomas**; Van Steirteghem, Andre; Devroey, Paul

CS (1) Centre Reproductive Med., Brussels Free Univ., Laarbeeklaan 101, 1090 Brussels Belgium

SO Fertility and Sterility, (Aug., 1998) Vol. 70, No. 2, pp. 357-359. ISSN: 0015-0282.

DT Article

LA English

AB Objective: To analyze the luteal phase of six patients undergoing controlled ovarian hyperstimulation (COH) with hMG and a new GnRH antagonist, **Cetrorelix**, without receiving luteal phase supplementation. Design: Phase II study involving the first six patients who did not receive luteal phase support. Setting: Tertiary referral center. Patient(s): Six healthy women undergoing COH for assisted reproductive techniques. Intervention(s): Oocyte retrieval was performed 36 hours after hCG administration, followed by embryo transfer 2 days later. No luteal phase supplementation was given. Main Outcome

Measure(s):

Serum E2, progesterone, LH, and FSH concentrations were measured.

Result(s): The length of the luteal phase was  $\leq 12$  days in three of the six patients. One of the patients in whom the luteal phase was  $>12$  days had a low serum progesterone concentration (2.9 ng/mL) on day 10. Serum LH concentrations decreased after the preovulatory hCG injection in all patients. However, a progressive increase in LH was observed after

day

7, reaching normal values. Conclusion(s): Corpus luteum function seems to be impaired in cycles that are stimulated with hMG and the GnRH

antagonist

**Cetrorelix**.

L10 ANSWER 10 OF 14 USPTFULL

AN 97:78416 USPTFULL

TI Products for administering an initial high dose of **Cetrorelix** and producing a combination package for use when treating diseases

IN **Engel, Jurgen**, Alzenau, Germany, Federal Republic of  
Hilgard, Peter, Frankfurt, Germany, Federal Republic of  
**Reissmann, Thomas**, Frankfurt, Germany, Federal Republic of

PA ASTA Medica Aktiengesellschaft, Dresden, Germany, Federal Republic of (non-U.S. corporation)

PI US 5663145 19970902

AI US 1994-354838 19941208 (8)

PRAI DE 1993-4342091 19931209

DT Utility

FS Granted

EXNAM Primary Examiner: Russel, Jeffrey E.

LREP Cushman Darby & Cushman IP Group of Pillsbury Madison & Sutro LLP

CLMN Number of Claims: 25  
ECL Exemplary Claim: 7  
DRWN No Drawings  
LN.CNT 227

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB For application during the treatment of benign and malign tumour diseases, the product according to the invention containing the initial dose of **Cetrorelix** acetate and one or more maintenance doses of **Cetrorelix** acetate, **Cetrorelix** embonate or a slow-release form of **Cetrorelix**, is used as a combination preparation for treatment to be administered at specific time intervals.

L10 ANSWER 11 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1  
AN 95280014 EMBASE  
DN 1995280014

TI Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of **infertility**: An overview.

AU **Reissmann Th.**; Felberbaum R.; Diedrich K.; Engel J.; Comaru-Schally A.M.; Schally A.V.

CS ASTA Medica AG, Frankfurt-M, Germany

SO Human Reproduction, (1995) 10/8 (1974-1981).

ISSN: 0268-1161 CODEN: HUREEE

CY United Kingdom

DT Journal; Article

FS 003 Endocrinology

010 Obstetrics and Gynecology

037 Drug Literature Index

038 Adverse Reactions Titles

LA English

SL English

AB Luteinizing hormone-releasing hormone (LHRH) plays a crucial role in controlling the ovarian cycle in women. By modification of the molecular structure of this decapeptide, analogues were synthesized with agonistic or antagonistic effects on the gonadotrophic cells of the anterior pituitary gland. The agonists, after an initial stimulatory effect

('flare up'), lead to desensitization of the gonadotrophic cells and a reduction in the number of LHRH receptors on the cell membrane ('down-regulation'), while the antagonists produce an immediate effect by competitive blockade of the LHRH receptors. After administration of LHRH antagonists, the

serum

levels of FSH and LH decrease within hours. Nevertheless, the adenohypophysis maintains its responsiveness to an LHRH stimulus ('pituitary response') after pretreatment with an antagonist. This different pharmacological mechanism of LHRH antagonists makes possible

new

approaches to ovarian stimulation and to the therapy of sex steroid dependent diseases. The premature LH surge, the main cause of

cancellation

during induction of superovulation in assisted reproduction technology (ART) programmes, can be abolished by short term application of an LHRH antagonist associated with a reduced human menopausal gonadotrophin (HMG) requirement for ovarian stimulation. A future approach to ART might be based on the combination of pretreatment with an LHRH antagonist and ovulation induction by native LHRH or an agonist. The severe side effects encountered with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, especially **Cetrorelix** which is presently used clinically in controlled phase II clinical studies.

L10 ANSWER 12 OF 14 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2

AN 1995:415178 BIOSIS

DN PREV199598429478

TI Preserved pituitary response under ovarian stimulation with HMG and GnRH

antagonists (**Cetrorelix**) in women with tubal **infertility**

AU Felberbaum, Ricardo E. (1); **Reissmann, Thomas**; Kuepker, Wolfgang; Bauer, Otmar; Al Hasani, Safaa; Diedrich, Christa; Diedrich, Klaus

CS (1) Dep. of Obstetrics and Gynecology, Medical Univ. of Luebeck, Luebeck Germany

SO European Journal of Obstetrics & Gynecology and Reproductive Biology, (1995) Vol. 61, No. 2, pp. 151-155. ISSN: 0301-2115.

DT Article

LA English

AB Objective: To examine the pituitary response in patients undergoing short-term application of the GnRH antagonist **Cetrorelix** in the mid-cycle phase for hypophysial suppression of premature LH surges within an IVF-program. Design: Twenty patients suffering from primary or secondary tubal **infertility** were stimulated with hMG from cycle day 2. From day 7 till ovulation induction **Cetrorelix** was administered in two different dose regimens (15 patients 3 mg s.c. daily; 5 patients 1 mg s.c. daily). Three hours before ovulation induction a GnRH test was performed using 25 mu-g of native GnRH and the pituitary response examined by measurement of the serum LH concentration after 30 min. Results: Premature LH surges could be avoided in the 3-mg group and in the 1-mg group, respectively. Due to this, none of the cycles had to be cancelled. Oestradiol profiles and ultrasound demonstrated a satisfactory follicular maturation. All patients showed pronounced suppression of the serum LH levels before ovulation induction. The mean increase of serum LH due to the performed GnRH test was 10 mIU/ml for the 3-mg group, while the average maximum in the 1-mg group was about 32.5 mIU/ml. Conclusions: The pituitary response is preserved by the treatment with the GnRH antagonist **Cetrorelix**. The extent of suppression of the adenohypophysis, as expressed by the different reactions on GnRH test, can be modulated by the dosage administered. This should allow ovulation induction by GnRH or one of its agonists instead of hCG, which could be beneficial in patients at high risk of Ovarian Hyperstimulation Syndrome (OHSS) and those suffering from Polycystic Ovary Disease (PCOD).

L10 ANSWER 13 OF 14 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
DUPLICATE

3

AN 1994-265229 [33] WPIDS

DNC C1994-121294

TI Freeze-dried peptide compsns. - prepd. by freeze drying soln. of peptide in aq. acetic acid.

DC B04

IN ENGEL, J; REISSMANN, T; **SAUERBIER, D**; WICHERT, B; BURKHARD, W; JUERGEN, E

PA (ASTA) ASTA MEDICA AG

CYC 32

PI EP 611572 A2 19940824 (199433)\* DE 5p  
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE  
DE 4305225 A1 19940825 (199433) 5p  
AU 9455235 A 19940825 (199436)  
NO 9400564 A 19940822 (199436)  
CA 2115943 A 19940820 (199439)  
CZ 9400312 A3 19940914 (199439)  
BR 9400617 A 19940927 (199440)  
SK 9400195 A3 19940907 (199440)  
FI 9400779 A 19940820 (199441)  
JP 06271476 A 19940927 (199443) 5p

ZA 9401136 A 19941026 (199444) 12p  
 HU 67117 T 19950228 (199514)  
 EP 611572 A3 19950111 (199538)  
 AU 671881 B 19960912 (199644)  
 CN 1112019 A 19951122 (199737)  
 SG 46632 A1 19980220 (199822)  
 BR 1101004 A3 19980512 (199828)  
 CZ 284314 B6 19981014 (199847)  
 NZ 314707 A 19990225 (199914)  
 CZ 285768 B6 19991117 (200002)  
 EP 611572 B1 20000607 (200032) DE  
 R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE  
 DE 59409389 G 20000713 (200037)  
 HU 218281 B 20000728 (200045)  
 RU 2145234 C1 20000210 (200048)  
 ES 2148247 T3 20001016 (200058)  
 TW 387812 A 20000421 (200061)  
 ADT EP 611572 A2 EP 1994-101672 19940204; DE 4305225 A1 DE 1993-4305225  
 19930219; AU 9455235 A AU 1994-55235 19940217; NO 9400564 A NO 1994-564  
 19940218; CA 2115943 A CA 1994-2115943 19940218; CZ 9400312 A3 CZ  
 1994-312  
 19940214; BR 9400617 A BR 1994-617 19940218; SK 9400195 A3 SK 1994-195  
 19940218; FI 9400779 A FI 1994-779 19940218; JP 06271476 A JP 1994-20532  
 19940217; ZA 9401136 A ZA 1994-1136 19940218; HU 67117 T HU 1994-481  
 19940218; EP 611572 A3 EP 1994-101672 19940204; AU 671881 B AU 1994-55235  
 19940217; CN 1112019 A CN 1994-101378 19940218; SG 46632 A1 SG 1996-6874  
 19940204; BR 1101004 A3 BR 1997-1101004 19970514; CZ 284314 B6 CZ  
 1994-312  
 19940214; NZ 314707 A Div ex NZ 1994-250906 19940217, NZ 1994-314707  
 19940217; CZ 285768 B6 CZ 1998-974 19940214; EP 611572 B1 EP 1994-101672  
 19940204, Related to EP 1999-102340 19940204; DE 59409389 G DE  
 1994-509389  
 19940204, EP 1994-101672 19940204; HU 218281 B HU 1994-481 19940218; RU  
 2145234 C1 RU 1994-5001 19940218; ES 2148247 T3 EP 1994-101672 19940204;  
 TW 387812 A TW 1994-100769 19940131  
 FDT AU 671881 B Previous Publ. AU 9455235; CZ 284314 B6 Previous Publ. CZ  
 9400312; NZ 314707 A Div ex NZ 250906; CZ 285768 B6 Previous Publ. CZ  
 9800974; EP 611572 B1 Related to EP 947200; DE 59409389 G Based on EP  
 611572; HU 218281 B Previous Publ. HU 67117; ES 2148247 T3 Based on EP  
 611572  
 PRAI DE 1993-4305225 19930219  
 AB EP 611572 A UPAB: 19991110  
 Freeze-dried compsns. comprising a peptide of 3-15 amino acid units and  
 opt. one or more matrix materials are characterised in that 1 pt. wt. of  
 the peptide is dissolved in 100-10,000 pts. wt. of acetic acid and then  
 transferred to water and the resulting soln. is freeze dried.  
 USE/ADVANTAGE - The compsns. esp. contain **cetrorelix** (EP  
 299402), which is used in the treatment of female **infertility**  
 (for controlling ovulation prior to isolating egg cells for in-vitro  
**fertilisation**) and for gonad protection in male patients (e.g.  
 undergoing radio- or chemotherapy). The aq. acetic acid soln. can be  
 sterilised by filtration without gelation or hydrolysis of the peptide.  
 Dwg.0/0  
  
 L10 ANSWER 14 OF 14 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.  
 AN 94179320 EMBASE  
 DN 1994179320  
 TI Introduction of LHRH-antagonists into the treatment of gynaecological  
 disorders.  
 AU **Reissmann Th.**; Diedrich K.; Comaru-Schally A.M.; Schally A.V.  
 CS Clinic Obstetrics and Gynaecology, University of Lubeck, Lubeck, Germany  
 SO Human Reproduction, (1994) 9/5 (767-769).  
 ISSN: 0268-1161 CODEN: HUREEE  
 CY United Kingdom  
 DT Journal; (Short Survey)

FS 010 Obstetrics and Gynecology  
021 Developmental Biology and Teratology  
030 Pharmacology  
037 Drug Literature Index  
LA English

=> s infertil? or fertil?

L12 687340 INFERTIL? OR FERTIL?

=> s l12 and cetrorelix

L13 229 L12 AND CETRORELIX

=> s l13 and (female or gonadotrpohin)

L14 141 L13 AND (FEMALE OR GONADOTRPOHIN)

=>

=>

=>

=>

=>

=>

=>

=>

YOU HAVE RECEIVED 8 CONSECUTIVE ARROW PROMPTS (=>)

The arrow (=>) is the system prompt, where you enter a command. For an explanation of system commands, files, formats, etc., enter "HELP" and the name of the item you want explained at an arrow prompt (=>). Enter "HELP COMMANDS" for a list of commands that can be used in this file. Enter "HELP MESSAGES" for a list of online explanations that are available. The "?" can be used as a synonym for "HELP".

Help is also available at any prompt, and after any error message. Enter "HELP" or "?" at a prompt to see an explanation of the options. After an error message, enter "HELP" or "?" at the next prompt and you will receive a more detailed explanation of the error and how to correct it.

Automatic help is also available. When AUHELP is 'ON', you will automatically receive help following an error message. For more information on AUHELP, enter "HELP SET AUHELP" at an arrow prompt (=>).

Users who need additional assistance can contact the Help Desk at their nearest STN Service Center. Enter "HELP STN" for information on STN Service Centers. You may also choose to contact the database representative for the file you are searching, for more detailed help on database content and search strategy. For information on how to contact database representatives for the current file, enter "HELP DESK" at an arrow prompt (=>).

IF YOU REQUIRE FURTHER HELP, PLEASE CONTACT YOUR LOCAL HELP DESK  
=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=>

=> d his

(FILE 'HOME' ENTERED AT 12:32:54 ON 17 JUL 2001)

FILE 'EMBASE, MEDLINE, BIOSIS, USPATFULL, JAPIO, WPIDS, CAPLUS,  
AGRICOLA,  
LIFESCI, BIOTECHDS, JICST-EPLUS' ENTERED AT 12:33:40 ON 17 JUL 2001

	E ENGEL JURGEN/AU
L1	209 S E3-E4
	E WICHERT BURKHARD/AU
L2	12 S E3-E4
	E SAUERBIAR DEITER/AU
	E SAUERBIER DEITER/AU
L3	42 S E2-E5
	E REISSMANN THOMAS/AU
L4	54 S E1-E4
L5	284 S L1-L4
L6	52 S L5 AND CETRORELIX
L7	38 DUP REM L6 (14 DUPLICATES REMOVED)
L8	11 S L7 AND (INFERTIL? OR FERTILI?)
L9	17 S L6 AND (INFERTIL? OR FERTIL?)
L10	14 DUP REM L9 (3 DUPLICATES REMOVED)
L11	1 S L10 AND GONADOTROPHIN?
L12	687340 S INFERTIL? OR FERTIL?
L13	229 S L12 AND CETRORELIX
L14	141 S L13 AND (FEMALE OR GONADOTRPOHIN)

=> s l13 and (female or gonadotrophin)

L15 165 L13 AND (FEMALE OR GONADOTROPHIN)

=> s l15 and hmg

L16 61 L15 AND HMG

=> dup rem l16

PROCESSING COMPLETED FOR L16

L17 27 DUP REM L16 (34 DUPLICATES REMOVED)

=> d bib ab 1-27

L17 ANSWER 1 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1

AN 2001139783 EMBASE

TI Comparison of LH concentrations in the early and mid-luteal phase in IVF cycles after treatment with **HMG** alone or in association with the GnRH antagonist **Cetrorelix**.

AU Tavaniotou A.; Albano C.; Smitz J.; Devroey P.

CS P. Devroey, AZ-VUB, Centre for Reproductive Medicine, Laarbeeklaan 101, 1090 Brussels, Belgium. paul.devroey@az.vub.ac.be

SO Human Reproduction, (2001) 16/4 (663-667).

Refs: 36

ISSN: 0268-1161 CODEN: HUREEE

CY United Kingdom

DT Journal; Article

FS 010 Obstetrics and Gynecology

003 Endocrinology

030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB Luteinizing hormone (LH) is mandatory for the maintenance of the corpus luteum. Ovarian stimulation for IVF has been associated with a defective luteal phase. The luteal phases of two groups of patients with normal menstrual cycles and no endocrinological cause of **infertility** were retrospectively analysed in IVF cycles. Thirty-one **infertile** patients stimulated with human menopausal gonadotrophins (**HMG**) for IVF to whom the **gonadotrophin**-releasing hormone (GnRH) antagonist **Cetrorelix** 0.25 mg was also administered to prevent the LH surge (group I) were compared with 31 **infertile** patients stimulated with **HMG** alone (group II). Despite differences in the stimulation outcome, luteal LH serum concentrations were similar in the two groups. LH values dropped from 2.3  $\pm$  1 IU/I on the day of human chorionic **gonadotrophin** (HCG) administration to 1.1  $\pm$  0.7 IU/I on day HCG + 2 in group I ( $P < 0.0001$ ) and from 5.1  $\pm$  3 to 1.2  $\pm$  1.7 IU/I ( $P < 0.0001$ ) in group II. In the mid-luteal phase, LH concentrations were low in both groups. Our results suggest that suppressed LH concentrations in the early and mid-luteal phase may not be attributed solely to the GnRH-antagonist administration. Pituitary LH secretion may be inhibited by supraphysiological steroid serum concentration via long-loop feedback and/or by the central action of the exogenously administered HCG via a short-loop mechanism.

L17 ANSWER 2 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 2001030138 EMBASE

TI The use of LHRH antagonist: Multiple-dose administration.

AU Ludwig M.; Felberbaum R.E.; Diedrich K.

CS Dr. R.E. Felberbaum, Dept. of Gynecology and Obstetrics, Medical University of Lubeck, Razteburger Allee 160, 23562 Lubeck, Germany

SO Infertility and Reproductive Medicine Clinics of North America, (2001) 12/1 (129-139).

Refs: 25



ISSN: 1047-9422 CODEN: IRMCF8

CY United States

DT Journal; General Review

FS 003 Endocrinology  
010 Obstetrics and Gynecology  
037 Drug Literature Index  
038 Adverse Reactions Titles

LA English

SL English

AB The multiple-dose antagonist protocol for ovarian stimulation in IVF cycles can be combined with **hMG** or recombinant FSH. The protocol has several advantages, such as a reduction in the rate of moderate-to-severe OHSS, a shorter stimulation period, and more comfort for patients. There are no hormonal withdrawal symptoms, and a spontaneous menstrual cycle can be used. Whether there is a reduced pregnancy rate in this protocol when compared with the long agonist protocol is still a matter of debate. A significant difference has not been shown in any study thus far. A possible effect of the antagonist on endometrial receptivity has been suggested. Experimental data and prospective studies must be awaited before this hypothesis can be proven.

L17 ANSWER 3 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 2001030137 EMBASE

TI GnRH antagonist in single-dose applications.

AU Olivennes F.; Fanchin R.; Rongieres-Bertrand C.; Bouchard P.; Frydman R.

CS Dr. F. Olivennes, Dept. of Obstetrics and Gynecology, A. Beclere Hospital,  
157, Rue de la Porte de Trivaux, 92140 Clamart Cedex, France

SO Infertility and Reproductive Medicine Clinics of North America, (2001) 12/1 (119-128).  
Refs: 27  
ISSN: 1047-9422 CODEN: IRMCF8

CY United States

DT Journal; General Review

FS 003 Endocrinology  
010 Obstetrics and Gynecology  
036 Health Policy, Economics and Management  
037 Drug Literature Index  
038 Adverse Reactions Titles

LA English

SL English

AB Use of the GnRH antagonist **Cetrorelix** in natural cycles associated with gonadotropins allowed the authors to reduce the rate of premature and endogenous LH surges and, subsequently, the cancellation rate. Stimulation was minimal, and the pregnancy rates in this preliminary report were satisfactory. If a larger study confirms the results of the natural cycle with **hMG** support, the association of spontaneous cycles and the GnRH antagonist single-dose administration could represent in selected indications a promising first-choice IVF treatment regimen, avoiding the complications and the risks of the ovarian stimulation protocols. The reduction of the cost and the benefit of the oocyte retrieval in an outpatient procedure are obvious. Successive cycles with an acceptable success rate could result in increased cumulative pregnancy rates. In controlled ovarian stimulation, different studies have confirmed the efficacy of a single dose of 3 mg of **Cetrorelix** to prevent premature LH surges when administered in the late follicular phase. The single-dose protocol is easy to use and ensures the patient's compliance. When compared with the long protocol using a depot formula of triptorelin, the IVF-ET results showed a shorter duration of treatment, less amount of **hMG** needed, and a lower occurrence of ovarian hyperstimulation

syndrome. The tolerance to **Cetrorelix** was excellent in all of the patients treated, with only mild and transitory reactions at the injection site. GnRH antagonists are already available for clinical use

in

some countries. These compounds are expected to change protocols of ovarian stimulation. If similar pregnancy rates are confirmed, the main advantage of these compounds will be the reduction of side effects and complication rates. They could also allow the design of softer

stimulation

protocols using clomiphene citrate and "natural cycles." GnRH antagonists will enable different ways of triggering ovulation with native GnRH and GnRH agonists.

L17 ANSWER 4 OF 27 MEDLINE

AN 2000482969 MEDLINE

DN 20425014 PubMed ID: 10966979

TI Embryo implantation and GnRH antagonists: GnRH antagonists do not activate

the GnRH receptor.

AU Mannaerts B; Gordon K

CS Organon, Oss, The Netherlands.. b.mannerts@organon.oss.akzonobel.nl

SO HUMAN REPRODUCTION, (2000 Sep) 15 (9) 1882-3.

Journal code: HRP; 8701199. ISSN: 0268-1161.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200010

ED Entered STN: 20001019

Last Updated on STN: 20001019

Entered Medline: 20001010

AB Recent suggestions that **gonadotrophin**-releasing hormone (GnRH) antagonists activate the GnRH receptor are discussed. Most of the studies cited in support of this suggestion are in-vitro studies, testing supra-pharmacological doses of GnRH analogues in cancer cell lines, whereas GnRH antagonists, e.g. ganirelix or **cetrorelix**, do not affect the steroidogenesis of human granulosa cells in vitro. In patients treated with GnRH antagonists prior to IVE or intracytoplasmic sperm injection (ICSI), oocyte maturity and **fertilization** rates are equal to those achieved following a long protocol of GnRH agonists. Although there is a tendency towards a lower pregnancy rate (not statistically significant) in the initial trials using GnRH antagonist with either recombinant FSH or human menopausal **gonadotrophin** (**HMG**) for ovarian stimulation, this new treatment option of GnRH antagonists facilitates short and simple treatment and improves the convenience and safety for the patient. As with GnRH agonists in the

past,

the clinical outcome of GnRH antagonist treatment will improve with time as more clinical experience is gained (learning curve) and the treatment protocol is optimized. Moreover, a GnRH agonist instead of human

chorionic

**gonadotrophin** (HCG) may be used for triggering ovulation and will decrease the cancellation rate and minimize the risk for developing ovarian hyperstimulation syndrome (OHSS).

L17 ANSWER 5 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2

AN 2000164435 EMBASE

TI Ovarian stimulation for assisted reproduction with **HMG** and concomitant midcycle administration of the GnRH antagonist **Cetrorelix** according to the multiple dose protocol: A prospective uncontrolled phase III study.

AU Felberbaum R.E.; Albano C.; Ludwig M.; Riethmuller-Winzen H.; Grigat M.; Devroey P.; Diedrich K.H.R.

CS Dr. R.E. Felberbaum, Dept. of Obstetrics and Gynaecology, Medical University of Lubeck, Lubeck, Germany

SO Human Reproduction, (2000) 15/5 (1015-1020).  
 Refs: 28  
 ISSN: 0268-1161 CODEN: HUREEE  
 CY United Kingdom  
 DT Journal; Article  
 FS 037 Drug Literature Index  
 010 Obstetrics and Gynecology  
 003 Endocrinology  
 038 Adverse Reactions Titles  
 LA English  
 SL English  
 AB A total of 346 women with normal ovulatory function was stimulated with human menopausal gonadotrophins (**HMG**) to attain ovarian stimulation for IVF or intracytoplasmic sperm injection (ICSI). Stimulation with **HMG** started on cycle day 2 or 3. After 6 days of stimulation, **Cetrorelix** in its minimum effective multiple dose of 0.25 mg/day, was administered daily until induction of ovulation. In total, 333 patients (96.2%) reached the day of HCG administration, and 324 (93.6%) underwent oocyte retrieval. A mean of 25.2 ampoules of **HMG** was applied for a mean of 10.4 days. **Cetrorelix** was administered for a mean time lapse of 5.7 days. The mean normal **fertilization** rate was 60% in the IVF group and 59% in the ICSI group. Seventy pregnancies were attained, reflecting an ongoing clinical pregnancy rate of 24% per transfer. The ongoing clinical implantation rate was 11.4%. Only three cases of raised luteinizing hormone (LH) ( $.gtoreq.10$  IU/l) with increased progesterone secretion ( $.gtoreq.1$  ng/ml) were observed after initiation of **Cetrorelix** administration, reflecting an incidence of premature luteinization of 0.9%. The abortion rate was 17%. The incidence of severe ovarian hyperstimulation syndrome (World Health Organization grade III) was as low as 0.6%.

L17 ANSWER 6 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3  
 AN 2000095892 EMBASE  
 TI Ovarian stimulation with **HMG**: Results of a prospective randomized phase III European study comparing the luteinizing hormone-releasing hormone (LHRH)-antagonist **cetrorelix** and the LHRH-agonist buserelin.  
 AU Albano C.; Felberbaum R.E.; Smitz J.; Riethmuller-Winzen H.; Engel J.; Diedrich K.; Devroey P.  
 CS Dr. C. Albano, Centre for Reproductive Medicine, Dutch-speaking Brussels Free Univ., Brussels, Belgium  
 SO Human Reproduction, (2000) 15/3 (526-531).  
 Refs: 22  
 ISSN: 0268-1161 CODEN: HUREEE  
 CY United Kingdom  
 DT Journal; Article  
 FS 010 Obstetrics and Gynecology  
 037 Drug Literature Index  
 LA English  
 SL English  
 AB In this prospective and randomized study, 188 patients received the luteinizing hormone-releasing hormone (LHRH) antagonist **cetrorelix**, and 85 patients the LHRH agonist buserelin to prevent endogenous luteinizing hormone (LH) surges during ovarian stimulation in in-vitro **fertilization** (IVF)/intracytoplasmic sperm injection (ICSI) cycles. Ultimately, 181 patients (96.3%) in the **cetrorelix** group, and 77 (90.6%) in the buserelin group, reached the day of the human chorionic gonadotrophin (HCG) injection. The mean number of human menopausal gonadotrophin (**HMG**) ampoules administered and the mean number of stimulation days with **HMG** were significantly less in the **cetrorelix** group than in the buserelin group ( $P < 0.01$ ). A rise in LH and progesterone concentrations

was observed in three of the 188 patients (1.6%) who received **cetrorelix**. On the day of the HCG administration, more follicles of a small diameter (11-14 mm) were observed in the buserelin group than in the **cetrorelix** group ( $P = 0.02$ ) and the mean serum oestradiol concentration was significantly higher in patients who received buserelin than in those who received **cetrorelix** ( $P < 0.01$ ). Similar results were observed in **fertilization**, cleavage and pregnancy rates in the two groups. In conclusion, the use of the LHRH antagonists might be considered more advantageous because of the short-term application needed to inhibit **gonadotrophin** secretion, so allowing a reduction in the treatment time in a clinically significant manner.

L17 ANSWER 7 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4  
 AN 2000041165 EMBASE  
 TI Prospective, randomized, controlled study of in vitro **fertilization**-embryo transfer with a single dose of a luteinizing hormone-releasing hormone (LH-RH) antagonist (**cetrorelix**) or a depot formula of an LH-RH agonist (triptorelin).  
 AU Olivennes F.; Belaisch-Allart J.; Emperaire J.C.; Dechaud H.; Alvarez S.; Moreau L.; Nicollet B.; Zorn J.R.; Bouchard P.; Frydman R.  
 CS Dr. F. Olivennes, Service Gynecologie-Obstetrique, Hopital A. Beclere,  
 157 Rue de la Porte De Trivaux, 92140 Clamart Cedex, France  
 SO Fertility and Sterility, (2000) 73/2 (314-320).  
 Refs: 22  
 ISSN: 0015-0282 CODEN: FESTAS  
 PUI S 0015-0282(99)00524-5  
 CY United States  
 DT Journal; Article  
 FS 010 Obstetrics and Gynecology  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 LA English  
 SL English  
 AB Objective: To confirm the value of a single dose of 3 mg of **cetrorelix** in preventing the occurrence of premature LH surges. Design: Multicenter randomized, prospective study. Setting: Reproductive medicine units. Patient(s): **Infertile** patients undergoing ovarian stimulation for IVF-ET. Intervention(s): A single dose of 3 mg of **cetrorelix** (Cetrotide; ASTA Medica, Frankfurt, Germany) (115 patients) was administered in the late follicular phase. A depot preparation of triptorelin (Decapeptyl; Ipsen-Biotech, Paris, France) was chosen as a control agent (39 patients). Ovarian stimulation was conducted with **hMG** (Menogon; Ferring, Kiel, Germany). Main Outcome Measure(s): Premature LH surges (LH level  $>10$  IU/L), progesterone level greater than 1 ng/L, and IVF results. Result(s): No LH surge occurred after **cetrorelix** administration. The patients in the **cetrorelix** group had a lower number of oocytes and embryos. The percentage of mature oocytes and **fertilization** rates were similar in both groups, and the pregnancy rates were not statistically different. The length of stimulation, number of **hMG** ampules administered, and occurrence of the ovarian hyperstimulation syndrome were lower in the **cetrorelix** group. Tolerance of **cetrorelix** was excellent. Conclusion(s): A **cetrorelix** single-dose protocol prevented LH surges in all patients studied. It compares favorably to the 'long protocol' and could be a protocol of choice in IVF-ET. Copyright (C) 2000 American Society for Reproductive Medicine.

L17 ANSWER 8 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5  
 AN 2000302500 EMBASE

TI GnRH antagonist in single-dose applications.  
 AU Olivennes F.; Ayoubi J.M.; Fanchin R.; Rongieres-Bertrand C.; Hamamah S.;  
 Bouchard P.; Frydman R.  
 CS F. Olivennes, Department of Obstetrics/Gynecology, A. Beclere Hopital,  
 157 Rue de la Porte de Trivaux, 92140 Clamart cedex, France  
 SO Human Reproduction Update, (2000) 6/4 (313-317).  
 Refs: 21  
 ISSN: 1355-4786 CODEN: HRUPF8  
 CY United Kingdom  
 DT Journal; Article  
 FS 003 Endocrinology  
 010 Obstetrics and Gynecology  
 030 Pharmacology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 LA English  
 SL English  
 AB Previous studies on ovarian stimulation have confirmed the efficacy of a  
 single dose of the **gonadotrophin**-releasing hormone (GnRH)  
 antagonist, **Cetrorelix**, in preventing premature LH surges. The  
 single-dose protocol is easy to use and assures patient compliance. When  
 compared with the long protocol using a depot administration of the GnRH  
 agonist, triptorelin, the IVF results in patients treated with  
**Cetrorelix** showed a shorter treatment duration, reduced amount of  
 human menopausal **gonadotrophin** (HMG) required and a  
 lower occurrence of ovarian hyperstimulation syndrome (OHSS). The  
 pregnancy rates did not differ significantly between the two treatments.  
 The use of **Cetrorelix** in natural cycles associated with  
 gonadotrophins reduced the rate of premature LH surges and, therefore,  
 the cancellation rate. The stimulation was minimal and the preliminary  
 pregnancy rates were satisfactory. If a larger study confirms the results  
 of the natural cycle with HMG support, the single-dose  
 administration of GnRH antagonist could represent an interesting  
 first-choice IVF treatment in selected indications. The tolerance of  
**Cetrorelix** was excellent in all patients, with only mild and  
 transitory reactions at the injection site. New GnRH antagonists are  
 already available for clinical use in some countries, and they will  
 certainly change ovarian stimulation protocols. If the pregnancy rates  
 are confirmed, the main advantages of these new compounds are the reduction  
 in side-effects and complications of the stimulation protocol; a clear  
 benefit to the patients.

L17 ANSWER 9 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6  
 AN 2000093694 EMBASE  
 TI No significant leukocytosis under controlled ovarian stimulation using  
 the LHRH antagonist **Cetrorelix** and recFSH.  
 AU Ludwig M.; Strik D.; Felberbaum R.; Al-Hasani S.; Diedrich K.  
 CS M. Ludwig, Department Gynecology/Obstetrics, Medical University of  
 Lubeck,  
 Ratzeburger Allee 160, 23538 Lubeck, Germany  
 SO European Journal of Obstetrics Gynecology and Reproductive Biology,  
 (2000)  
 89/2 (177-179).  
 Refs: 10  
 ISSN: 0301-2115 CODEN: EOGRAL  
 PUI S 0301-2115(99)00195-5  
 CY Ireland  
 DT Journal; Article  
 FS 010 Obstetrics and Gynecology  
 025 Hematology

003 Endocrinology  
030 Pharmacology  
037 Drug Literature Index

LA English

SL English

AB Objective: To study the influence of an LHRH (luteinizing hormone releasing hormone) antagonist protocol (**Cetrorelix**) and the use of recombinant follicle-stimulating hormone (FSH) on the development of leukocytosis, compared to the use of urinary **HMG** (human menopausal **gonadotrophin**). Design: Prospective, randomized phase III clinical trial. Setting: **Infertility** day clinic, Department of Gynecology and Obstetrics. Patients: Thirty patients undergoing IVF/intracytoplasmic sperm injection (ICSI) treatment following controlled ovarian stimulation using a multiple dose protocol and the LHRH antagonist **Cetrorelix**. Main outcome measure: Differences in white blood cell (WBC) count before stimulation, during the follicular phase and in the midluteal phase. Results: Statistically significant increase in WBC count in the **HMG** group from the start of stimulation to the midluteal phase. No statistically significant increase in the recFSH group, but only a trend towards higher values was observed. Conclusion: The development of a leukocytosis in controlled ovarian stimulation does not depend on the protocol used. Urinary gonadotrophins seem to have a greater potential to increase WBC count compared to recombinant gonadotrophins. Copyright (C) 2000 Elsevier Science Ireland Ltd.

L17 ANSWER 10 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2000:458002 BIOSIS

DN PREV2000000458002

TI The use of GnRH antagonist for COH as a second line strategy in IVF or ICSI.

AU van Os, H. C. (1); Jansen, C. A. M. (1)

CS (1) Department of IVF, Reinier de Graaf Hospital Group, loc Diaconessenhuis Voorburg, Zaandam Netherlands

SO Human Reproduction (Oxford), (June, 2000) Vol. 15, No. Abstract Book 1, pp. 134. print.

Meeting Info.: 16th Annual Meeting of the European Society of Human Reproduction and Embryology Bologna, Italy June 25-28, 2000 European Society of Human Reproduction and Embryology  
. ISSN: 0268-1161.

DT Conference

LA English

SL English

L17 ANSWER 11 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2000:457980 BIOSIS

DN PREV2000000457980

TI Ovarian stimulation in poor responders using GnRH antagonists.

AU Nikolettos, N. (1); Al-Hasani, S.; Felberbaum, R.; Kupker, W.; Schopper, B.; Sturm, R.; Diedrich, K.

CS (1) Faculty of Medicine, Democritus University of Thrace, Alexandroupolis Greece

SO Human Reproduction (Oxford), (June, 2000) Vol. 15, No. Abstract Book 1, pp. 125. print.

Meeting Info.: 16th Annual Meeting of the European Society of Human Reproduction and Embryology Bologna, Italy June 25-28, 2000 European Society of Human Reproduction and Embryology  
. ISSN: 0268-1161.

DT Conference

LA English

SL English

L17 ANSWER 12 OF 27 MEDLINE  
 AN 2001033462 MEDLINE  
 DN 20457105 PubMed ID: 11000511  
 TI Comparison of cryopreservation outcome with human pronuclear stage oocytes obtained by the GnRH antagonist, **cetrorelix**, and GnRH agonists.  
 AU Nikolettos N; Al-Hasani S; Felberbaum R; Demirel L C; Riethmuller-Winzen H; Reissmann T; Schopper B; Sturm R; Diedrich K  
 CS Democritus University of Thrace, Faculty of Medicine, Alexandroupolis, Greece.  
 SO EUROPEAN JOURNAL OF OBSTETRICS, GYNECOLOGY, AND REPRODUCTIVE BIOLOGY, (2000 Nov) 93 (1) 91-5.  
 Journal code: E4L. ISSN: 0301-2115.  
 CY Ireland  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 200011  
 ED Entered STN: 20010322  
 Last Updated on STN: 20010322  
 Entered Medline: 20001130  
 AB This retrospective study was performed to examine the implantation and pregnancy rates of frozen-thawed pronuclear stage oocytes obtained with the use of a GnRH antagonist, **Cetrorelix** (Cetrotide(R)) ASTA-Medica, Frankfurt/M, Germany) used in a multidose protocol with **hMG**, and to compare these results with those obtained after a conventional long GnRH analogue protocol (Decapeptyl-Depot, Ferring, Kiel, Germany). The study population consisted of 31 **infertile** couples with frozen-thawed pronuclear stage oocytes after ICSI treatment using the GnRH antagonist **Cetrorelix** (**Cetrorelix**(R)) and 31 **infertile** couples with frozen-thawed pronuclear stage oocytes after ICSI treatment using the long GnRH analogue protocol. Patients underwent ICSI after down regulation with a GnRH agonist (Decapeptyl) and stimulation with **hMG**, or a GnRH antagonist (**Cetrorelix**) and **hMG**. The supernumerary pronuclear stage oocytes were cryopreserved and transferred in a later mildly stimulated cycle. The implantation and pregnancy rates for frozen-thawed pronuclear stage oocytes derived from the GnRH antagonist compared with the GnRH agonist were 3.26% versus 3.73% (P=1.0000) and 8.33% versus 10.25% (P=1.0000), respectively. To our knowledge we report here the first pregnancies obtained by the transfer of cryopreserved pronuclear stage embryos generated from ICSI using a GnRH antagonist in the collecting cycle. The use of **Cetrorelix** in a multiple dose protocol in combination with **hMG** does not demonstrate a negative effect on viability, implantation potential or pregnancy outcome as compared to 2PN conceptuses obtained from a long GnRH agonist-**hMG** protocol.

L17 ANSWER 13 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 7  
 AN 1999201422 EMBASE  
 TI Luteal phase and clinical outcome after human menopausal gonadotrophin/gonadotrophin releasing hormone antagonist treatment for ovarian stimulation in in-vitro fertilization /intracytoplasmic sperm injection cycles.  
 AU Albano C.; Smits J.; Tournaye H.; Riethmuller-Winzen H.; Van Steirteghem A.; Devroey P.  
 CS C. Albano, Center for Reproductive Medicine, University Hospital Medical School, Dutch-speaking Brussels Free Univ., Laarbeeklaan 101, 1090 Brussels, Belgium  
 SO Human Reproduction, (1999) 14/6 (1426-1430).  
 Refs: 36  
 ISSN: 0268-1161 CODEN: HUREEE  
 CY United Kingdom

DT Journal; Article  
 FS 003 Endocrinology  
 010 Obstetrics and Gynecology  
 037 Drug Literature Index  
 LA English  
 SL English  
 AB The luteal phase hormonal profile and the clinical outcome of 69 patients undergoing in-vitro **fertilization** (IVF) or intracytoplasmic sperm injection (ICSI) after ovarian stimulation with human menopausal **gonadotrophin** (HMG) and the **gonadotrophin**-releasing hormone (GnRH) antagonist **Cetrorelix** were analysed. Twenty-four patients received **Cetrorelix** 0.5 mg (group I) while in 45 patients **Cetrorelix** 0.25 mg was administered (group II). Human chorionic **gonadotrophin** (HCG) was used as luteal support. Nine clinical pregnancies were obtained in group I (37.5%) and 12 in group II (26.6%). These results were not significantly different. Serum progesterone and oestradiol concentrations did not differ between the two groups either in pregnant or non-pregnant patients. An expected decrease of the same hormones was observed 8 days after the preovulatory HCG injection in non-pregnant women. With regard to serum luteinizing hormone concentrations, a decrease was observed 2 days after the pre-ovulatory injection and was maintained at almost undetectable levels throughout the entire luteal phase in both conception and non-conception cycles of group I and group II. This study demonstrates that different doses of GnRH antagonist do not have any impact on the luteal phase of IVF/ICSI cycles when hormonal support is given.

HCG

L17 ANSWER 14 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 8  
 AN 1999133653 EMBASE  
 TI Is there a difference in the function of granulosa-luteal cells in patients undergoing in-vitro **fertilization** either with **gonadotrophin**-releasing hormone agonist or **gonadotrophin**-releasing hormone antagonist?.

AU Lin Y.; Kahn J.A.; Hillensjo T.  
 CS J.A. Kahn, Department Obstetrics Gynaecology, University Hospital of Trondheim, N-7006 Trondheim, Norway  
 SO Human Reproduction, (1999) 14/4 (885-888).  
 Refs: 21  
 ISSN: 0268-1161 CODEN: HUREEE

CY United Kingdom  
 DT Journal; Article  
 FS 002 Physiology  
 021 Developmental Biology and Teratology  
 037 Drug Literature Index  
 LA English  
 SL English  
 AB **Gonadotrophin**-releasing hormone (GnRH) regulates **gonadotrophin** release. It has been shown that GnRH may have a direct effect on the ovary, as the addition of GnRH to granulosa cell cultures inhibits the production of progesterone and oestradiol. Specific GnRH receptors have been found to be present in rat and human granulosa cells. Desensitization of the pituitary by GnRH agonist has become common in in-vitro **fertilization** (IVF) treatment, usually by a long protocol of 2-3 weeks. With the introduction of GnRH antagonists, which produce an immediate blockage of the GnRH receptors, a much shorter exposure is needed of 3-6 days. The aim of this study was to evaluate the effect of a GnRH agonist (buserelin) and a GnRH antagonist (**cetrorelix**) on the function of granulosa cells cultured in vitro from IVF patients. Women were treated by IVF randomized either to have buserelin nasal spray from the luteal phase in the previous cycle or **cetrorelix** from day 6 of the cycle. Both groups had ovarian stimulation with human menopausal **gonadotrophin** (HMG) 150 IU daily, i.e. HCG was administered when the follicles were larger



than 17 mm, and aspirated 36 h later. Granulosa cells, separated and washed from large follicles containing ova, were pooled. After 48 h of pre-incubation, the granulosa cells were cultured for 4 days in medium with either added testosterone or cAMP with or without HCG, with change of medium after 2 days. The progesterone and oestradiol concentrations in the culture medium were measured by immunological assay, and cellular protein was measured by microprotein assay. The results showed that granulosa cells from women treated with GnRH antagonist (**Cetrorelix**) responded earlier to the in-vitro hormone stimulation in terms of progesterone accumulation than women treated with the GnRH agonist (buserelin). This may have been due to difference in time of exposure to the analogue. The results may indicate that the luteal function is less impaired in GnRH antagonist treatment than in GnRH agonist treatment.

L17 ANSWER 15 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 9  
AN 1999100542 EMBASE

TI Revival of the natural cycles in in-vitro **fertilization** with the use of a new **gonadotrophin**-releasing hormone antagonist ( **Cetrorelix**): A pilot study with minimal stimulation.

AU Rongieres-Bertrand C.; Olivennes F.; Righini C.; Fanchin R.; Taieb J.; Hamamah S.; Bouchard P.; Frydeman R.

CS F. Olivennes, Department Obstetrics and Gynecology, A. Beclere Hospital, 157 Rue de la Porte de Trivaux, 92140 Clamart Cedex, France

SO Human Reproduction, (1999) 14/3 (683-688).  
Refs: 54

ISSN: 0268-1161 CODEN: HUREEE

CY United Kingdom

DT Journal; Article

FS 010 Obstetrics and Gynecology  
030 Pharmacology  
037 Drug Literature Index

LA English

SL English

AB Natural cycles were abandoned in in-vitro **fertilization** (IVF) embryo transfer, due to premature luteinizing hormone (LH) surges - and subsequent high cancellation rates. In this study, we investigated the administration of a new **gonadotrophin**-releasing hormone antagonist (**Cetrorelix**) in the late follicular phase of natural cycles in patients undergoing IVF and intracytoplasmic sperm injection (ICSI). A total of 44 cycles from 33 healthy women [mean age 34.1 +/-

1.4 (range 26-36) years] were monitored, starting on day 8 by daily ultrasound

and measurement of serum concentrations of oestradiol, LH, follicle stimulating hormone (FSH) and progesterone. When plasma oestradiol concentrations reached 100-150 pg/ml, with a lead follicle between 12-14 mm diameter, a single injection (s.c.) of 0.5 mg (19 cycles) or 1 mg (25 cycles) **Cetrorelix** was administered. Human menopausal **gonadotrophin** (HMG; 150 IU) was administered daily at the time of the first injection of **Cetrorelix**, and repeated thereafter until human chorionic **gonadotrophin** (HCG) administration. Four out of 44 cycles were cancelled (9.0%). No decline

in follicular growth or oestradiol secretion was observed after **Cetrorelix** administration. A total of 40 oocyte retrievals leading to 22 transfers (55%) was performed. In 10 cycles (25%), no oocyte was obtained. **Fertilization** failure despite ICSI occurred in six cycles (15%). In two patients the embryo was arrested at the 2 pronuclear (PN) stage. The stimulation was minimal (4.7 +/- 1.4 HMG ampoules). A total of seven clinical pregnancies was obtained (32.0% per transfer, 17.5% per retrieval), of which five are ongoing. Thus, a spontaneous cycle and the GnRH antagonist **Cetrorelix** in single dose administration could represent a first-choice IVF treatment with

none

of the complications and risks of current controlled ovarian hyperstimulation protocols, and an acceptable success rate.

- L17 ANSWER 16 OF 27 BIOSIS COPYRIGHT 2001 BIOSIS  
AN 1999:392736 BIOSIS  
DN PREV199900392736  
TI A prospective randomized study comparing the use of **HMG** versus rec-FSH with the single dose GnRH antagonist (**Cetrorelix**) protocol in IVF-embryo transfer.  
AU Olivennes, F. (1); Belaich-Allart, J.; Alvarez, S.; Bouchard, P.; Frydman, R. (1)  
CS (1) Obstetric and Gynecologic Department, Hospital A. Beclere, Clamart France  
SO Human Reproduction (Oxford), (June, 1999) Vol. 14, No. ABSTR. BOOK 1, pp. 61.  
Meeting Info.: 15th Annual Meeting of the European Society of Human Reproduction and Embryology and the Annual Meeting of the Federation Francaise pour l'Etude de la Reproduction Tours, France June 26-30, 1999  
European Society of Human Reproduction and Embryology  
. ISSN: 0268-1161.  
DT Conference  
LA English
- L17 ANSWER 17 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 10  
AN 1998262426 EMBASE  
TI The luteal phase of nonsupplemented cycles after ovarian superovulation with human menopausal gonadotropin and the gonadotropin-releasing hormone antagonist **Cetrorelix**.  
AU Albano C.; Grimbizis G.; Smits J.; Riethmuller-Winzen H.; Reissmann T.; Van Steirteghem A.; Devroey P.  
CS Dr. C. Albano, Centre for Reproductive Medicine, Brussels Free University,  
Laarbeeklaan 101, 1090 Brussels, Belgium. LR1AAOC@AZ.VUB.AC.BE  
SO Fertility and Sterility, (1998) 70/2 (357-359).  
Refs: 4  
ISSN: 0015-0282 CODEN: FESTAS  
PUI S 0015-0282(98)00135-6  
CY United States  
DT Journal; Article  
FS 010 Obstetrics and Gynecology  
037 Drug Literature Index  
LA English  
SL English  
AB Objective: To analyze the luteal phase of six patients undergoing controlled ovarian hyperstimulation (COH) with **hMG** and a new GnRH antagonist, **Cetrorelix**, without receiving luteal phase supplementation. Design: Phase II study involving the first six patients who did not receive luteal phase support. Setting: Tertiary referral center. Patient(s): Six healthy women undergoing COH for assisted reproductive techniques. Intervention(s): Oocyte retrieval was performed 36 hours after hCG administration, followed by embryo transfer 2 days later. No luteal phase supplementation was given. Main Outcome Measure(s):  
Serum E2, progesterone, LH, and FSH concentrations were measured.  
Result(s): The length of the luteal phase was .ltoreq.12 days in three of the six patients. One of the patients in whom the luteal phase was >12 days had a low serum progesterone concentration (2.9 ng/mL) on day 10. Serum LH concentrations decreased after the preovulatory hCG injection in all patients. However, a progressive increase in LH was observed after day 7, reaching normal values. Conclusion(s): Corpus luteum function seems to be impaired in cycles that are stimulated with **hMG** and the GnRH antagonist **Cetrorelix**.

L17 ANSWER 18 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.  
 AN 1998311417 EMBASE  
 TI New approaches to ovarian stimulation.  
 AU Diedrich K.; Felberbaum R.; Jones H.; Brinsden P.; Edwards R.G.; Howles C.; Cohen J.; Fanchin R.; Oehninger S.  
 CS K. Diedrich, Department Obstetrics Gynecology, Medical University of Lubeck, Ratzeburger Allee 160, 23538 Lubeck, Germany  
 SO Human Reproduction, (1998) 13/SUPPL. 3 (1-17).  
 Refs: 44  
 ISSN: 0268-1161 CODEN: HUREEE  
 CY United Kingdom  
 DT Journal; Conference Article  
 FS 010 Obstetrics and Gynecology  
 037 Drug Literature Index  
 LA English  
 SL English  
 AB Suppression of endogenous hormone production by **gonadotrophin**-releasing hormone (GnRH) agonists followed by controlled ovarian hyperstimulation (COH) with human gonadotrophins, especially the so-called 'long protocol' has developed from second-line into first-line therapy. Due to this attitude premature luteinization can be safely avoided, enhancing therapeutic efficacy. Recombinant preparations of human follicle stimulating hormone (FSH) have been proven to be effective within COH according to the long protocol. The high purity of these compounds may have clinical advantages. GnRH antagonists could be successfully introduced in COH protocols. Also, daily injections in the midcycle phase according to the 'Lubeck protocol', as single or only dual administrations around day 9 seem to abolish any premature LH rises. Due to their different pharmacological mode of action, based on a classic competitive receptor blockage GnRH antagonists avoid any flare-up period and allow ovarian stimulation to start within the spontaneous cycle. Pregnancy rates are comparable to those after long protocol stimulation. Combination of softer stimulation regimes like clomiphene citrate and low dose **HMG** with midcycle administration of GnRH antagonists may be the way to a cheap, safe and efficient ovarian stimulation. It seems to be high time for modest forms of ovarian stimulation, lowering burden and risk for our patients.

L17 ANSWER 19 OF 27 MEDLINE  
 AN 97277516 MEDLINE  
 DN 97277516 PubMed ID: 9130900  
 TI Comparison of different doses of gonadotropin-releasing hormone antagonist **Cetrorelix** during controlled ovarian hyperstimulation.  
 AU Albano C; Smits J; Camus M; Riethmuller-Winzen H; Van Steirteghem A; Devroey P  
 CS Centre for Reproductive Medicine, Dutch-speaking Brussels Free University, Belgium.  
 SO FERTILITY AND STERILITY, (1997 May) 67 (5) 917-22.  
 Journal code: EVF; 0372772. ISSN: 0015-0282.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199705  
 ED Entered STN: 19970523  
 Last Updated on STN: 19970523  
 Entered Medline: 19970515  
 AB OBJECTIVE: To assess the minimal effective dose of a GnRH antagonist (**Cetrorelix**; Asta Medical; Frankfurt, Germany) to prevent premature

LH surge in patients undergoing controlled ovarian hyperstimulation (COH) for assisted reproductive technologies. DESIGN: In 69 patients COH was carried out with the association of hMG, starting on day 2 of the menstrual cycle, and a GnRH antagonist (**Cetrorelix**) was administered from day 6 of the hMG treatment (day 7 of the menstrual cycle) every day up to and including the last day of the hMG injection. In 32 and 30 patients, 0.5 mg and 0.25 mg of **Cetrorelix** were administered, respectively. Seven patients received 0.1 mg of **Cetrorelix**. SETTING: Tertiary referral center. RESULT(S): No premature endogenous LH surge occurred in patients treated with 0.5 and 0.25 mg of **Cetrorelix**, and serum LH concentrations were maintained constantly low during the entire follicular phase in both groups. Follicle-stimulating hormone, LH, E2, and P expressed as area under the curve were similar in both groups. A premature LH surge (18 mIU/mL; conversion factor to SI unit, 1.00) with a concomitant P rise (1.7 micrograms/L; conversion factor to SI unit, 3.180) occurred in one of the seven patients treated with 0.1 mg **Cetrorelix**; therefore, treatment with this dose was discontinued. CONCLUSION(S): The minimal effective dose of **Cetrorelix** able to prevent premature LH surge in COH cycles is 0.25 mg administered daily.

- L17 ANSWER 20 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 11  
 AN 96357183 EMBASE  
 DN 1996357183  
 TI Hormonal profile during the follicular phase in cycles stimulated with a combination of human menopausal **gonadotrophin** and **gonadotrophin**-releasing hormone antagonist (**Cetrorelix**).  
 AU Albano C.; Smitz J.; Camus M.; Riethmuller-Winzen H.; Siebert-Weigel M.; Diedrich K.; Van Steirteghem A.C.; Devroey P.  
 CS Centre for Reproductive Medicine, University Hospital Medical School, Dutch-speaking Brussels Free Univ., Laarbeeklaan 101, 1090 Brussels, Belgium  
 SO Human Reproduction, (1996) 11/10 (2114-2118).  
 ISSN: 0268-1161 CODEN: HUREEE  
 CY United Kingdom  
 DT Journal; Article  
 FS 010 Obstetrics and Gynecology  
 037 Drug Literature Index  
 LA English  
 SL English  
 AB A third-generation **gonadotrophin**-releasing hormone antagonist (**Cetrorelix**) was used during ovarian stimulation in 32 patients undergoing assisted reproduction, in order to prevent the premature luteinizing hormone (LH) surge. In all patients, ovarian stimulation was carried out with two or three ampoules of human menopausal **gonadotrophin** (HMG), starting on day 2 of the menstrual cycle. In addition, 0.5 mg of **Cetrorelix** was administered daily from day 6 of HMG treatment until the day of ovulation induction by human chorionic **gonadotrophin** (HCG). A significant drop in plasma LH concentration was observed within a few hours of the first administration of **Cetrorelix** ( $P < 0.005$ ). Moreover, no LH surge was detected at any point in the treatment period in any of the 32 patients. A mean oestradiol concentration of 2122  $\pm$  935 ng/l was observed on the day of the HCG administration, indicating normal folliculogenesis. Like LH, progesterone concentration also dropped within a few hours of the first administration of **Cetrorelix** ( $P < 0.005$ ). A 0.5 mg daily dose of **Cetrorelix** prevented a premature LH surge in all the 32 patients treated.
- L17 ANSWER 21 OF 27 MEDLINE  
 AN 96324678 MEDLINE  
 DN 96324678 PubMed ID: 8671476

TI Subtle progesterone rise after the administration of the **gonadotrophin**-releasing hormone antagonist **cetrorelix** in intracytoplasmic sperm injection cycles.  
 AU Ubaldi F; Albano C; Peukert M; Riethmuller-Winzen H; Camus M; Smits J; Van Steirteghem A; Devroey P  
 CS Centre for Reproductive Medicine, Dutch-speaking Brussels Free University, Brussels, Belgium.  
 SO HUMAN REPRODUCTION, (1996 Jul) 11 (7) 1405-7.  
 Journal code: HRP; 8701199. ISSN: 0268-1161.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199611  
 ED Entered STN: 19961219  
 Last Updated on STN: 19961219  
 Entered Medline: 19961106  
 AB In the present study, subtle serum progesterone rise ( $\geq 1.1$  ng/ml) during the late follicular phase is reported, for the first time to our knowledge, in patients using a potent **gonadotrophin**-releasing hormone (GnRH) antagonist, **Cetrorelix**, in combination with human menopausal **gonadotrophin** (hMG) for ovarian stimulation prior to intracytoplasmic sperm injection (ICSI). In five out of 24 patients (20%) serum progesterone levels were  $\geq 1.1$  ng/ml. The cycle characteristics of the patients were similar in both groups. No premature endogenous luteinizing hormone (LH) surge occurred and the serum LH concentrations were constantly low during the follicular phase. The 17-beta oestradiol and follicle stimulating hormone (FSH) exposure were higher in cycles with premature luteinization. The greater oestradiol and FSH exposure confirm that one of the possible factors inducing subtle serum progesterone rise is the increased oestradiol and FSH-induced LH receptivity in granulosa cells.

L17 ANSWER 22 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 12  
 AN 96083720 EMBASE  
 DN 1996083720  
 TI Hormone profiles under ovarian stimulation with human menopausal gonadotropin (hMG) and concomitant administration of the gonadotropin releasing hormone (GnRH)-antagonist **Cetrorelix** at different dosages.  
 AU Felberbaum R.; Reissmann T.; Kupker W.; Al-Hasani S.; Bauer O.; Schill T.; Zoll C.; Diedrich C.; Diedrich K.  
 CS Department of Obstetrics/Gynecology, Medical University of Lubeck, Ratzeburger Allee 160, 23538 Lubeck, Germany  
 SO Journal of Assisted Reproduction and Genetics, (1996) 13/3 (216-222).  
 ISSN: 1058-0468 CODEN: JARGE4  
 CY United States  
 DT Journal; Article  
 FS 010 Obstetrics and Gynecology  
 037 Drug Literature Index  
 038 Adverse Reactions Titles  
 LA English  
 SL English  
 AB Purpose: The premature LH surge in ART programs seems to be avoided by daily administration of the GnRH-antagonist **Cetrorelix** during the midcycle phase in controlled ovarian hyperstimulation with hMG. The dosage necessary for sufficient suppression of the pituitary gland is not yet defined. Methods: To elucidate this question three daily dosages (3, 1, 0.5 mg) were administered and the hormone profiles obtained as well as the number of oocytes retrieved, the **fertilization**

rate, and the consumption of **HMG** were compared. Results: No premature LH surge could be observed at any of the three dosages administered. Both gonadotropins were deeply suppressed. The **fertilization** rates of the oocytes obtained were 45.3% in the 3-mg group, 53.1% in the 1-mg group, and 67.7% in the 0.5-mg group. The average uses of **hMG** ampoules were 30 in the 3-mg group, 27 in the 1-mg group, and 26 in the 0.5-mg group. Conclusions: Cetrolix, 0.5 mg/day, administered during the midcycle phase of controlled ovarian hyperstimulation with **hMG** is enough to prevent completely the premature LH surge. Perhaps even lower dosages would be sufficient. Regarding **fertilization** rates and use of **hMG**, the lower dosage seems to be the most favorable.

L17 ANSWER 23 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 13

AN 95280014 EMBASE

DN 1995280014

TI Development and applications of luteinizing hormone-releasing hormone antagonists in the treatment of **infertility**: An overview.

AU Reissmann Th.; Felberbaum R.; Diedrich K.; Engel J.; Comaru-Schally A.M.; Schally A.V.

CS ASTA Medica AG, Frankfurt-M, Germany

SO Human Reproduction, (1995) 10/8 (1974-1981).

ISSN: 0268-1161 CODEN: HUREEE

CY United Kingdom

DT Journal; Article

FS 003 Endocrinology

010 Obstetrics and Gynecology

037 Drug Literature Index

038 Adverse Reactions Titles

LA English

SL English

AB Luteinizing hormone-releasing hormone (LHRH) plays a crucial role in controlling the ovarian cycle in women. By modification of the molecular structure of this decapeptide, analogues were synthesized with agonistic or antagonistic effects on the gonadotrophic cells of the anterior pituitary gland. The agonists, after an initial stimulatory effect ('flare up'), lead to desensitization of the gonadotrophic cells and a reduction in the number of LHRH receptors on the cell membrane ('down-regulation'), while the antagonists produce an immediate effect by competitive blockade of the LHRH receptors. After administration of LHRH antagonists, the

serum

levels of FSH and LH decrease within hours. Nevertheless, the adenohypophysis maintains its responsiveness to an LHRH stimulus ('pituitary response') after pretreatment with an antagonist. This different pharmacological mechanism of LHRH antagonists makes possible

new

approaches to ovarian stimulation and to the therapy of sex steroid dependent diseases. The premature LH surge, the main cause of

cancellation

during induction of superovulation in assisted reproduction technology (ART) programmes, can be abolished by short term application of an LHRH antagonist associated with a reduced human menopausal **gonadotrophin** (**HMG**) requirement for ovarian stimulation.

pretreatment

A future approach to ART might be based on the combination of with an LHRH antagonist and ovulation induction by native LHRH or an agonist. The severe side effects encountered with early LHRH antagonists, such as anaphylactoid reactions due to histamine release, are almost completely eliminated in modern antagonists, especially **Cetrorelix** which is presently used clinically in controlled phase II clinical studies.

L17 ANSWER 24 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 14

AN 95213899 EMBASE  
 DN 1995213899  
 TI Preserved pituitary response under ovarian stimulation with **HMG** and GnRH antagonists (**Cetrorelix**) in women with tubal **infertility**.  
 AU Felberbaum R.E.; Reissmann T.; Kupke W.; Bauer O.; Al Hasani S.; Diedrich C.; Diedrich K.  
 CS Department of Obstetrics/Gynecology, Medical University of Lubeck, Lubeck, Germany  
 SO European Journal of Obstetrics Gynecology and Reproductive Biology, (1995) 61/2 (151-155).  
 ISSN: 0028-2243 CODEN: EOGRAL  
 CY Ireland  
 DT Journal; Article  
 FS 010 Obstetrics and Gynecology  
 037 Drug Literature Index  
 LA English  
 SL English  
 AB Objective: To examine the pituitary response in patients undergoing short-term application of the GnRH antagonist **Cetrorelix** in the mid-cycle phase for hypophysial suppression of premature LH surges within an IVF-program. Design: Twenty patients suffering from primary or secondary tubal **infertility** were stimulated with **hMG** from cycle day 2. From day 7 till ovulation induction **Cetrorelix** was administered in two different dose regimens (15 patients 3 mg s.c. daily; 5 patients 1 mg s.c. daily). Three hours before ovulation induction a GnRH test was performed using 25 .mu.g of native GnRH and the pituitary response examined by measurement of the serum LH concentration after 30 min. Results: Premature LH surges could be avoided in the 3-mg group and in the 1-mg group, respectively. Due to this, none of the cycles had to be cancelled. Oestradiol profiles and ultrasound demonstrated a satisfactory follicular maturation. All patients showed pronounced suppression of the serum LH levels before ovulation induction. The mean increase of serum LH due to the performed GnRH test was 10 mIU/ml for the 3-mg group, while the average maximum in the 1-mg group was about 32.5 mIU/ml. Conclusions: The pituitary response is preserved by the treatment with the GnRH antagonist **Cetrorelix**. The extent of suppression of the adenohypophysis, as expressed by the different reactions on GnRH test, can be modulated by the dosage administered. This should allow ovulation induction by GnRH or one of its agonists instead of hCG, which could be beneficial in patients at high risk of Ovarian Hyperstimulation Syndrome (OHSS) and those suffering from Polycystic Ovary Disease (PCOD).

L17 ANSWER 25 OF 27 MEDLINE  
 AN 96213256 MEDLINE  
 DN 96213256 PubMed ID: 8672908  
 TI [GnRH antagonists in gynecology: initial results within the scope of controlled ovarian hyperstimulation].  
 Die GnRH-Antagonisten in der Gynakologie: Erste Ergebnisse im Rahmen der kontrollierten ovariellen Hyperstimulation (COH).  
 AU Felberbaum R; Reissmann T; Zoll C; Kupker W; al-Hasani S; Diedrich C; Diedrich K  
 CS Klinik fur Frauenheilkunde und Geburtshilfe der Medizinischen Universitat zu Lubeck.  
 SO GYNAKOLOGISCH-GEBURTSHILFLICHE RUNDSCHAU, (1995) 35 Suppl 1 113-7.  
 Journal code: BK6; 9212667. ISSN: 1018-8843.  
 CY Switzerland  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA German  
 FS Priority Journals

EM 199608  
ED Entered STN: 19960822  
Last Updated on STN: 19960822  
Entered Medline: 19960812  
AB OBJECTIVE: Applicability of the GnRH-antagonist **Cetrorelix** within controlled ovarian hyperstimulation (COH) to avoid the premature LH-surge should be examined. METHODS: 35 patients suffering from tubal **infertility** were stimulated for In Vitro **Fertilization** (IVF) by human menopausal gonadotrophins (**HMG**) and concomitant administration of **Cetrorelix** in different dosages (3 mg, 1 mg, 0,5 mg). RESULTS: No premature LH-surge could be observed. CONCLUSIONS: Short term administration of the GnGR-antagonists avoids the occurrence of a premature LH-surge.

L17 ANSWER 26 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 15  
AN 94179324 EMBASE  
DN 1994179324

TI Suppression of the endogenous luteinizing hormone surge by the **gonadotrophin-releasing hormone antagonist Cetrorelix** during ovarian stimulation.  
AU Diedrich K.; Diedrich C.; Santos E.; Zoll C.; Al-Hasani S.; Reissmann T.; Krebs D.; Klingmuller D.  
CS Clinic Gynaecology and Obstetrics, University of Lubeck, Lubeck, Germany  
SO Human Reproduction, (1994) 9/5 (788-791).  
ISSN: 0268-1161 CODEN: HUREEE  
CY United Kingdom  
DT Journal; Article  
FS 003 Endocrinology  
010 Obstetrics and Gynecology  
030 Pharmacology  
037 Drug Literature Index

LA English

SL English

AB Surges of luteinizing hormone (LH) that result in luteinization but occur prematurely with respect to the diameter of the leading follicle, prevent attempts to induce multiple follicular maturation for in-vitro **fertilization** (IVF) in a significant number of women. We examined the possibility of blocking premature LH surges by the administration of **Cetrorelix** a potent antagonist of **gonadotrophin**-releasing hormone (GnRH), in a study including 20 patients, some of whom had previously shown premature LH surges. All patients were treated with human menopausal gonadotrophins (**HMG**) starting on day 2. From day 7 until the induction of ovulation by human chorionic **gonadotrophin** (HCG) the GnRH antagonist **Cetrorelix** was given daily. HCG was injected when the dominant follicle had reached a diameter of .gtoreq.18 mm and oestradiol concentration was >300 pg/ml for each follicle having a diameter of >15 mm. Oocyte collection was

performed

36 h later by transvaginal ultrasound puncture, followed by IVF and embryo

transfer. The hormone profiles of these patients and the results of IVF and embryo transfer are comparable to those treated with GnRH agonists and

**HMG**. However, less time and especially less **HMG** is needed in comparison to patients stimulated with a long agonist protocol. Hence, treatment with **Cetrorelix** proved to be much more comfortable for the patient. In this study we showed that combined treatment with gonadotrophins and the GnRH antagonist **Cetrorelix** is a promising method for ovarian stimulation in patients who frequently exhibit premature LH surges and therefore fail to complete treatment.

L17 ANSWER 27 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 16  
AN 94277948 EMBASE  
DN 1994277948



TI The single or dual administration of the gonadotropin-releasing hormone antagonist **Cetrorelix** in an in vitro **fertilization**-embryo transfer program.

AU Olivennes F.; Fanchir R.; Bouchard P.; De Ziegler D.; Taieb J.; Selva J.; Frydman R.

CS Dept. of Obstetrics and Gynecology, Antoine Beclere Hospital, 157, rue de la porte de trivaux, 92141 Clamart Cedex, France

SO Fertility and Sterility, (1994) 62/3 (468-476).  
ISSN: 0015-0282 CODEN: FESTAS

CY United States

DT Journal; Article

FS 010 Obstetrics and Gynecology  
037 Drug Literature Index

LA English

SL English

AB Objective: To assess the ability of a GnRH antagonist (**Cetrorelix**, Asta Medica AG, Frankfurt, Germany) to prevent premature LH surges in an IVF-ET program using a simple protocol with one or two administrations. Design: Controlled ovarian hyperstimulation was carried out in 17 women with three ampules a day of **hMG**, starting on day 2 of the menstrual cycle. A dose of 5 mg of **Cetrorelix** was administered when plasma E2 levels were between 150 and 200 pg/mL (conversion factor to SI unit, 3.671) per follicle of .gtoreq. 14 mm. A second injection was performed 48 hours later if the triggering of ovulation was not decided in the meantime. Results: Six patients received one injection and 11 patients received two administrations. Plasma LH levels showed a marked decrease and remained low after the administration of the GnRH antagonist. In six patients, the first administration of **Cetrorelix** was performed when a significant rise in LH plasma level was present. Even in these patients the GnRH antagonist was able to prevent an LH surge. The tolerance of the product was good. Six clinical pregnancies were obtained, of which four are ongoing (25% per ET). Two ongoing pregnancies were obtained after the transfer of a frozen-thawed embryo (35.3% per retrieval). Conclusions: The GnRH antagonist **Cetrorelix** in a simple, unique or dual administration, protocol was able to prevent premature LH surge in all of the 17 patients studied. If these results are confirmed by larger, randomized studies, the good tolerance and efficacy that we observed suggest a bright future for this product in assisted reproductive technologies.

=> d his

(FILE 'HOME' ENTERED AT 12:32:54 ON 17 JUL 2001)

FILE 'EMBASE, MEDLINE, BIOSIS, USPATFULL, JAPIO, WPIDS, CAPLUS, AGRICOLA, LIFESCI, BIOTECHDS, JICST-EPLUS' ENTERED AT 12:33:40 ON 17 JUL 2001

	E ENGEL JURGEN/AU
L1	209 S E3-E4
	E WICHERT BURKHARD/AU
L2	12 S E3-E4
	E SAUERBIAR DEITER/AU
	E SAUERBIER DEITER/AU
L3	42 S E2-E5
	E REISSMANN THOMAS/AU
L4	54 S E1-E4
L5	284 S L1-L4

L6 52 S L5 AND CETRORELIX  
 L7 38 DUP REM L6 (14 DUPLICATES REMOVED)  
 L8 11 S L7 AND (INFERTIL? OR FERTILI?)  
 L9 17 S L6 AND (INFERTIL? OR FERTIL?)  
 L10 14 DUP REM L9 (3 DUPLICATES REMOVED)  
 L11 1 S L10 AND GONADOTROPHIN?  
 L12 687340 S INFERTIL? OR FERTIL?  
 L13 229 S L12 AND CETRORELIX  
 L14 141 S L13 AND (FEMALE OR GONADOTRPOHIN)  
 L15 165 S L13 AND (FEMALE OR GONADOTROPHIN)  
 L16 61 S L15 AND HMG  
 L17 27 DUP REM L16 (34 DUPLICATES REMOVED)

=> s l13 and (hexitol or mannitol or glucitol or sorbitol or dulcitol or allitol or iditol or urea or sodium chloride)

7 FILES SEARCHED...

L18 8 L13 AND (HEXITOL OR MANNITOL OR GLUCITOL OR SORBITOL OR DULCITO  
 L OR ALLITOL OR IDITOL OR UREA OR SODIUM CHLORIDE)

=> s l18 and bulking agent

L19 0 L18 AND BULKING AGENT

=> dup rem l18

PROCESSING COMPLETED FOR L18

L20 7 DUP REM L18 (1 DUPLICATE REMOVED)

=> d bib ab 1-7

L20 ANSWER 1 OF 7 USPATFULL DUPLICATE 1  
 AN 2001:14464 USPATFULL  
 TI Pharmaceutical formulations for sustained drug delivery  
 IN Gefter, Malcolm L., Lincoln, MA, United States  
 Barker, Nicholas, Southborough, MA, United States  
 Musso, Gary, Hopkinton, MA, United States  
 Molineaux, Christopher J., Brookline, MA, United States  
 PA Praecis Pharmaceuticals, Inc., Cambridge, MA, United States (U.S.  
 corporation)  
 PI US 6180608 B1 20010130  
 AI US 1997-988851 19971211 (8)  
 RLI Continuation-in-part of Ser. No. US 1996-762747, filed on 11 Dec 1996,  
 now patented, Pat. No. US 5968895  
 DT Utility  
 FS Granted  
 EXNAM Primary Examiner: Cintins, Marianne M.; Assistant Examiner:  
 Delacroix-Muirheid, C.  
 LREP Lahive & Cockfield, LLP, DeConti, Jr., Giulio A., Laccotripe, Maria C.  
 CLMN Number of Claims: 50  
 ECL Exemplary Claim: 1  
 DRWN 8 Drawing Figure(s); 5 Drawing Page(s)  
 LN.CNT 1333  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB Sustained delivery formulations comprising a water-insoluble complex of  
 a peptidic compound (e.g., a peptide, polypeptide, protein,  
 peptidomimetic or the like) and a carrier macromolecule are disclosed.  
 The formulations of the invention allow for loading of high  
 concentrations of peptidic compound in a small volume and for delivery  
 of a pharmaceutically active peptidic compound for prolonged periods,  
 e.g., one month, after administration of the complex. The complexes of  
 the invention can be milled or crushed to a fine powder. In powdered  
 form, the complexes form stable aqueous suspensions and dispersions,  
 suitable for injection. In a preferred embodiment, the peptidic  
 compound

of the complex is an LHRH analogue, preferably an LHRH antagonist, and the carrier macromolecule is an anionic polymer, preferably carboxymethylcellulose. Methods of making the complexes of the invention, and methods of using LHRH-analogue-containing complexes to treat conditions treatable with an LHRH analogue, are also disclosed.

L20 ANSWER 2 OF 7 USPATFULL

AN 2001:52022 USPATFULL

TI GnRH antagonists being modified in positions 5 and 6

IN Semple, Graeme, Gothenburg, Sweden

Jiang, Guangcheng, San Diego, CA, United States

PA Ferring BV, Hoofddorp, Netherlands (non-U.S. corporation)

PI US 6214798 B1 20010410

WO 9846634 19981022

AI US 2000-402698 20000103 (9)

WO 1998-US7438 19980413

20000103 PCT 371 date

20000103 PCT 102(e) date

RLI Continuation-in-part of Ser. No. US 1997-837042, filed on 11 Apr 1997, now patented, Pat. No. US 5925730

DT Utility

FS Granted

EXNAM Primary Examiner: Jones, Dwayne C.; Assistant Examiner: Delacroix-Muirheid, C.

LREP Fitch, Even, Tabin & Flannery

CLMN Number of Claims: 20

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1463

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Peptides are provided which have improved duration of GnRH antagonistic properties. These antagonists may be used to regulate **fertility** and to treat steroid-dependent tumors and for other short-term and long-term treatment indications. These antagonists have a derivative of aminoPhe or its equivalent in the 5- or the 5- and 6-positions. This derivative is modified so as to contain a carbamoyl group or heterocycle, including a **urea** moiety, in its side chain. Decapeptides having the formula:

Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(L-hydroorotyl)-D-4Amf(Q.sub.2)-Leu-Lys(isopropyl)-Pro-Xaa.sub.10,

wherein Q.sub.2 is Cbm or MeCbm and Xaa.sub.10 is D-Ala-ol or Ala-ol

are

particularly effective and continue to exhibit very substantial suppression of LH secretion at 96 hours following injection.

L20 ANSWER 3 OF 7 USPATFULL

AN 1999:128511 USPATFULL

TI Pharmaceutical formulations for sustained drug delivery

IN Gefter, Malcolm L., Lincoln, MA, United States

Barker, Nicholas, Southborough, MA, United States

Musso, Gary, Hopkinton, MA, United States

Molineaux, Christopher J., Brookline, MA, United States

PA Praecis Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)

PI US 5968895 19991019

AI US 1996-762747 19961211 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Richter, Johann; Assistant Examiner: Delacroix-Muirheid, C.

LREP Lahive & Cockfield, LLP, Mandragouras, Amy E., DeConti, Giulio A.

CLMN Number of Claims: 32

ECL Exemplary Claim: 10

DRWN 2 Drawing Figure(s); 2 Drawing Page(s)

LN.CNT 775

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Sustained delivery formulations comprising a water-insoluble complex of a peptide and a carrier macromolecule are disclosed. The formulations of the invention allow for loading of high concentrations of peptide in a small volume and for delivery of a pharmaceutically active peptide for prolonged periods, e.g., one month, after administration of the complex.

The complexes of the invention can be milled or crushed to a fine powder. In powdered form, the complexes form stable aqueous suspensions and dispersions, suitable for injection. In a preferred embodiment, the peptide of the complex is an LHRH analogue, preferably an LHRH antagonist, and the carrier macromolecule is an anionic polymer, preferably carboxymethylcellulose. Methods of making the complexes of the invention, and methods of using LHRH-analogue-containing complexes to treat conditions treatable with an LHRH analogue, are also disclosed.

L20 ANSWER 4 OF 7 USPATFULL

AN 1999:81921 USPATFULL

TI GnRH antagonists

IN Semple, Graeme, Hampshire, United Kingdom  
Jiang, Guangcheng, San Diego, CA, United States

PA Ferring BV, Hoofddorp, Netherlands (non-U.S. corporation)

PI US 5925730 19990720

AI US 1997-837042 19970411 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Hill, Jr., Robert J.; Assistant Examiner:  
Delacroix-Muirheid, C.

LREP Fitch, Even, Tabin & Flannery

CLMN Number of Claims: 21

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 1458

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Peptides are provided which have improved duration of GnRH antagonistic properties. These antagonists may be used to regulate **fertility** and to treat steroid-dependent tumors and for other short-term and long-term treatment indications. These antagonists have a derivative of aminoPhe or its equivalent in the 5- and/or 6-positions. This derivative

contains a carbamoyl group or a heterocycle including a **urea** in its side chain. Particularly effective decapeptides, which continue to exhibit very substantial suppression of LH secretion at 96 hours following injection, have the formulae: Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2, and Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(hydroorotyl)-D-4Amf(Q.sub.2)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2, wherein Q.sub.2 is Cbm or MeCbm.

L20 ANSWER 5 OF 7 USPATFULL

AN 1998:124554 USPATFULL

TI GnRH antagonist decapeptides

IN Jiang, Guangcheng, San Diego, CA, United States  
Semple, Graeme, Hampshire, United Kingdom

PA Ferring BV, Hoofddorp, Netherlands (non-U.S. corporation)

PI US 5821230 19981013

AI US 1997-837041 19970411 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Wang, Cecilia F.

LREP Fitch, Even, Tabin & Flannery

CLMN Number of Claims: 20  
ECL Exemplary Claim: 1  
DRWN No Drawings  
LN.CNT 1630

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Peptides are provided which have improved duration of GnRH antagonistic properties and/or which can be synthesized more economically. These antagonists may be used in the same manner as the compounds of which they are analogs to regulate **fertility** and to treat steroid-dependent tumors and for other short-term and long-term treatment indications. One particularly effective peptide, a decapeptide

analog of the GnRH antagonist Acyline, has the formula:

Ac-D-2Nal-D-4Cpa-D-Dpr(methylcarbamoyl)-Ser-4Aph(acetyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2. It continues to exhibit very substantial suppression of LH secretion at 96 hours following injection.

Other economically attractive and pharmacologically effective analogs have the formulas: Ac-D-2Nal-D-4Cpa-Xaa.sub.3 -Ser-4Aph(acetyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2 ; and Ac-D-2Nal-D-4Cpa-Xaa.sub.3 -Ser-4Aph(hydroorotyl)-D-4Aph(acetyl)-Leu-Lys(isopropyl)-Pro-D-Ala-NH.sub.2, wherein Xaa.sub.3 is D-Gln or Gln.

L20 ANSWER 6 OF 7 USPATFULL

AN 97:78416 USPATFULL

TI Products for administering an initial high dose of **Cetrorelix** and producing a combination package for use when treating diseases

IN Engel, Jurgen, Alzenau, Germany, Federal Republic of  
Hilgard, Peter, Frankfurt, Germany, Federal Republic of  
Reissmann, Thomas, Frankfurt, Germany, Federal Republic of

PA ASTA Medica Aktiengesellschaft, Dresden, Germany, Federal Republic of (non-U.S. corporation)

PI US 5663145 19970902

AI US 1994-354838 19941208 (8)

PRAI DE 1993-4342091 19931209

DT Utility

FS Granted

EXNAM Primary Examiner: Russel, Jeffrey E.

LREP Cushman Darby & Cushman IP Group of Pillsbury Madison & Sutro LLP

CLMN Number of Claims: 25

ECL Exemplary Claim: 7

DRWN No Drawings

LN.CNT 227

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB For application during the treatment of benign and malign tumour diseases, the product according to the invention containing the initial dose of **Cetrorelix** acetate and one or more maintenance doses of **Cetrorelix** acetate, **Cetrorelix** embonate or a slow-release form of **Cetrorelix**, is used as a combination preparation for treatment to be administered at specific time intervals.

L20 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2001 ACS

AN 1994:587330 CAPLUS

DN 121:187330

TI Preparation of a **cetrorelix** lyophilized composition

IN Engel, Juergen; Sauerbier, Dieter; Wichert, Burkhard; Reissmann, Thomas

PA Asta Medica AG, Germany

SO Eur. Pat. Appl., 5 pp.

CODEN: EPXXDW

DT Patent

LA German

FAN.CNT 1

PATENT NO.

KIND DATE

APPLICATION NO. DATE

PI	EP 611572	A2	19940824	EP 1994-101672	19940204
	EP 611572	A3	19950111		
	EP 611572	B1	20000607		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,				
SE	DE 4305225	A1	19940825	DE 1993-4305225	19930219
	EP 947200	A2	19991006	EP 1999-102340	19940204
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				
IE	AT 193653	E	20000615	AT 1994-101672	19940204
	ES 2148247	T3	20001016	ES 1994-101672	19940204
	CZ 284314	B6	19981014	CZ 1994-312	19940214
	CZ 285768	B6	19991117	CZ 1998-974	19940214
	AU 9455235	A1	19940825	AU 1994-55235	19940217
	AU 671881	B2	19960912		
	JP 06271476	A2	19940927	JP 1994-20532	19940217
	PL 177177	B1	19991029	PL 1994-302266	19940217
	CA 2115943	AA	19940820	CA 1994-2115943	19940218
	FI 9400779	A	19940820	FI 1994-779	19940218
	NO 9400564	A	19940822	NO 1994-564	19940218
	ZA 9401136	A	19940829	ZA 1994-1136	19940218
	BR 9400617	A	19940927	BR 1994-617	19940218
	HU 67117	A2	19950228	HU 1994-481	19940218
	HU 218281	B	20000728		
	CN 1112019	A	19951122	CN 1994-101378	19940218
	RU 2145234	C1	20000210	RU 1994-5001	19940218
PRAI	DE 1993-4305225	A	19930219		
	EP 1994-101672	A3	19940204		
AB	A lyophilizate of a peptide with 3-15 amino acid residues (e.g. <b>cetrorelix</b> ) and .gtoreq.1 optional matrix materials (e.g. <b>mannitol</b> ) is prepd. by dissolving in 100-10,000 wt. parts AcOH, dilg. with water, and lyophilizing the resulting soln. The lyophilizate is useful for prepn. of a medication for treatment of female <b>infertility</b> and protection of the gonads from the follicular hyperstimulation seen with other <b>infertility</b> treatments.				

=> d clm 1 2

L20 ANSWER 1 OF 7 USPATFULL

DUPLICATE 1

CLM What is claimed is:

1. A packaged formulation for treating a subject for a condition treatable with an LHRH analogue, comprising: a solid ionic complex of

an LHRH analogue and a carrier macromolecule packaged with instructions for fusing the complex for treating a subject having a condition treatable with an LHRH analogue, wherein the peptide content of said complex is 57% to 80% by weight.

2. The packaged formulation of claim 1, wherein the LHRH analogue has the following structure: Ac-D-Nal.sup.1, 4-Cl-D-Phe.sup.2, D-Pal.sup.3, N-Me-Tyr.sup.5, D-Asn.sup.6, Lys(iPr).sup.8, D-Ala.sup.10 -LHRH, and

the carrier macromolecule is carboxymethylcellulose, or a pharmaceutically acceptable salt thereof.

3. In a syringe having a lumen, the improvement comprises, inclusion of a liquid suspension of a solid ionic complex of an LHRH analogue and a carrier macromolecule in the lumen, wherein the peptide content of said complex is 57% to 80% by weight.

4. The syringe of claim 3, wherein the LHRH analogue has the following structure: Ac-D-Nal.sup.1, 4-Cl-D-Phe.sup.2, D-Pal.sup.3,

the N-Me-Tyr.<sup>5</sup>, D-Asn.<sup>6</sup>, Lys(iPr).<sup>8</sup>, D-Ala.<sup>10</sup> -LHRH, and carrier macromolecule is carboxymethylcellulose, or a pharmaceutically acceptable salt thereof.

5. A method for treating a subject for a condition treatable with an LHRH analogue, comprising administering to the subject a pharmaceutical formulation comprising a solid ionic complex of an LHRH analogue and a carrier macromolecule, wherein the peptide content of said complex is 57% to 80% by weight.

6. The method of claim 5, wherein the complex provides sustained delivery of the LHRH analogue to a subject for at least one week after the pharmaceutical composition is administered to the subject.

7. The method of claim 5, wherein the complex provides sustained delivery of the LHRH analogue to a subject for at least two weeks after the pharmaceutical composition is administered to the subject.

8. The method of claim 5, wherein the complex provides sustained delivery of the LHRH analogue to a subject for at least three weeks after the pharmaceutical composition is administered to the subject.

after 9. The method of claim 5, wherein the complex provides sustained delivery of the LHRH analogue to a subject for at least four weeks the pharmaceutical composition is administered to the subject.

10. The method of claim 5, wherein the LHRH analogue is an LHRH antagonist.

11. The method of claim 10, wherein the LHRH antagonist has the following structure: Ac-D-Nal.<sup>1</sup>, 4-Cl-D-Phe.<sup>2</sup>, D-Pal.<sup>3</sup>, N-Me-Tyr.<sup>5</sup>, D-Asn.<sup>6</sup>, Lys(iPr).<sup>8</sup>, D-Ala.<sup>10</sup> -LHRH.

12. The method of claim 5, wherein the carrier macromolecule is an anionic polymer.

13. The method of claim 5, wherein the carrier macromolecule is an anionic polyalcohol derivative, or fragment thereof, or a pharmaceutically acceptable salt thereof.

14. The method of claim 5, wherein the carrier macromolecule is an anionic polysaccharide derivative, or fragment thereof, or a pharmaceutically acceptable salt thereof.

15. The method of claim 5, wherein the carrier macromolecule is carboxymethylcellulose, or a pharmaceutically acceptable salt thereof.

selected 16. The method of claim 5, wherein the carrier macromolecule is from the group consisting of align, alginate, anionic acetate polymers, anionic acrylic polymers, xantham gums, anionic carageenan derivatives, anionic polygalacturonic acid derivatives, sodium starch glycolate, and fragments, derivatives and pharmaceutically acceptable salts thereof.

17. The method of claim 5, wherein the pharmaceutical formulation is administered to the subject by a parenteral route.

18. The method of claim 5, wherein the pharmaceutical formulation is administered to the subject orally.

19. The method of claim 5, wherein the pharmaceutical formulation is administered by intramuscular injection or subcutaneous/intradermal injection.

20. The method of claim 5, wherein the condition treatable with an LHRH analogue is a hormone dependent cancer.
21. The method of claim 20, wherein the hormone dependent cancer is prostate cancer.
22. The method of claim 5, wherein the condition treatable with an LHRH analogue is selected from the group consisting of benign prostatic hypertrophy, precocious puberty, endometriosis and uterine fibroids.
23. The method of claim 5, wherein the LHRH analogue is administered for in vitro **fertilization** or contraceptive purposes.
24. A pharmaceutical composition comprising a solid ionic complex of a pharmaceutically active peptide and a carrier macromolecule, wherein the peptide content of said complex is 57% to 80% by weight.
25. A pharmaceutical composition consisting essentially of a solid ionic complex of a pharmaceutically active peptide and a carrier macromolecule, wherein the peptide content of said complex is 57% to 80% by weight.
26. The pharmaceutical composition of any one of claim 24 or 25, wherein the pharmaceutically active peptide is cationic and the carrier macromolecule is anionic.
27. The pharmaceutical composition of any one of claim 24 or 25, wherein the pharmaceutically active peptidic compound is anionic and the carrier macromolecule is cationic.
28. The pharmaceutical composition of any one of claim 24 or 25, wherein the complex provides sustained delivery of the pharmaceutically active peptide to a subject for at least one week after the pharmaceutical composition is administered to the subject.
29. The pharmaceutical composition of any one of claim 24 or 25, wherein the complex provides sustained delivery of the pharmaceutically active peptide to a subject for at least two weeks after the pharmaceutical composition is administered to the subject.
30. The pharmaceutical composition of any one of claim 24 or 25, wherein the complex provides sustained delivery of the pharmaceutically active peptide to a subject for at least three weeks after the pharmaceutical composition is administered to the subject.
31. The pharmaceutical composition of any one of claim 24 or 25, wherein the complex provides sustained delivery of the pharmaceutically active peptide to a subject for at least four weeks after the pharmaceutical composition is administered to the subject.
32. The pharmaceutical composition of any one of claim 24 or 25, wherein the pharmaceutically active peptide is a multivalent cationic or anionic



peptide.

33. The pharmaceutical composition of any one of claim 24 or 25, wherein the peptide is 5 to 20 amino acids in length.

34. The pharmaceutical composition of any one of claim 24 or 25, wherein the peptide is 1 to 15 amino acids in length.

35. The pharmaceutical composition of any one of claim 24 or 25, wherein the peptide is 8 to 12 amino acids in length.

36. The pharmaceutical composition of any one of claim 24 or 25, wherein the carrier macromolecule is an anionic polymer.

37. The pharmaceutical composition of any one of claim 24 or 25, wherein the carrier macromolecule is an anionic polyalcohol derivative, or fragment thereof.

38. The pharmaceutical composition of any one of claim 24 or 25, wherein the carrier macromolecule is an anionic polysaccharide derivative, or fragment thereof.

39. The pharmaceutical composition of any one of claim 24 or 25, wherein the carrier macromolecule is carboxymethylcellulose, or a fragment or derivative thereof.

40. The pharmaceutical composition of any one of claim 24 or 25, wherein the carrier macromolecule is selected from the group consisting of align, alginate, anionic acetate polymers, anonic acrylic polymers, xantham gums, anionic carageenan derivatives, anionic polygalacturonic acid derivatives, sodium starch glycolate, and fragments, derivatives and pharmaceutically acceptable salts thereof.

41. The pharmaceutical composition of any one of claim 24 or 25, which is a lyophilized solid.

42. The pharmaceutical composition of any one of claim 24 or 25, wherein said solid ionic complex is suspended as a liquid suspension or dispersed as a semi-solid dispersion.

43. The pharmaceutical composition of any one of claim 24 or 25, wherein said pharmaceutically active peptide is an LHRH analogue.

44. The pharmaceutical composition of claim 43 wherein the LHRH analogue is an LHRH antagonist comprising a peptide compound, wherein a residue of the peptide compound corresponding to the amino acid at position 6 of natural mammalian LHRH comprises a D-asparagine structure.

45. The pharmaceutical composition of claim 43 wherein the LHRH analogue is an LHRH antagonist comprising a peptide compound comprising a structure: A-B-C-D-E-F-G-H-I-J wherein A is pyro-Glu, Ac-D-Nal, Ac-D-Qal, Ac-Sar, or Ac-D-Pal B is His or 4-Cl-D-Phe C is Trp, D-Pal,

Arg

D-Nal, L-Nal, D-Pal(N-O), or D-Trp D is Ser E is N-Me-Ala, Tyr, N-Me-Tyr, Ser, Lys(iPr), 4-Cl-Phe, His, Asn, Met, Ala, Arg or Ile; F is D-Asn, D-Gln, or D-Thr; G is Leu or Trp; H is Lys(iPr), Gln, Met, or

I is Pro; and J is Gly-NH.sub.2 or D-Ala-NH.sub.2 ; or a pharmaceutically acceptable salt thereof.

46. The pharmaceutical composition of claim 43, wherein the LHRH analogue is an LHRH antagonist having the following structure: Ac-D-Nal.sup.1, 4-Cl-D-Phe.sup.2, D-Pal.sup.3, N-Me-Tyr.sup.5, D-Asn.sup.6, Lys(iPr).sup.8, D-Ala.sup.10 -LHRH.

47. The pharmaceutical composition of claim 43 wherein said pharmaceutically active peptide is an LHRH antagonist.

48. The pharmaceutical composition of claim 43, wherein the LHRH analogue is the LHRH agonist Leuprolide having the structure pGlu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro(ethylamide)-Gly.

49. The pharmaceutical composition of claim 43, wherein the LHRH analogue is the LHRH antagonist **Cetrorelix** having the structure Ac-D-Nal-4-Cl-D-Phe-D-Pal-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala.

50. The pharmaceutical composition of any one of claim 24 or 25, wherein said pharmaceutically active peptide is selected from the group consisting of bradykinin analogues, parathyroid hormone, adenocorticotrophic hormone, calcitonin, and vasopressin analogues.

L20 ANSWER 2 OF 7 USPATFULL

CLM What is claimed is:

1. A GnRH antagonist peptide having the formula: X-D-2Nal-(A)D-Phe-D-3Pal-Ser-Xaa.sub.5 -Xaa.sub.6 -Leu-Xaa.sub.8 -Pro-Xaa.sub.10 or a pharmaceutically acceptable salt thereof wherein: X is an acyl group having not more than 7 carbon atoms or Q, with Q being ##STR11## and with R being H or lower alkyl; A is 4Cl, 4F, 4Br, 4NO.sub.2, 4CH.sub.3, 4OCH.sub.3, 3,4Cl.sub.2 or C.sup..alpha. Me4Cl; Xaa.sub.5 is 4Aph(Q.sub.1) or 4Amf(Q.sub.1) with Q.sub.1 being ##STR12## a D/L mixture of either, Xaa.sub.6 is D-4Aph(Q.sub.2), D-4Amf(Q.sub.2), D-Lys(Nic), D-Cit, D-Hci or D-3Pal, with Q.sub.2 being For, Ac, 3-amino-1,2,4-triazole(atz), Q or Q.sub.1 ; Xaa.sub.8 is Lys(iPr), Arg, Har, Arg(Et.sub.2) or Har(Et.sub.2); and Xaa.sub.10 is D-Ala-ol or Ala-ol; provided however that the .alpha.-amino group of Xaa.sub.5 may optionally be methylated; and provided further that when Xaa.sub.6 contains D- or L-Hor or D- or L-Imz or a D/L mixture of either, Xaa.sub.5 may have Ac, For or 3-amino-1,2,4-triazole as Q.sub.1.

2. A GnRH antagonist peptide according to claim 1 wherein Q is carbamoyl or methylcarbamoyl.

3. A GnRH antagonist according to claim 1 wherein Q.sub.1 is L-Hor or D-Hor.

4. A GnRH antagonist according to claim 1 wherein X is Ac and Xaa.sub.8 is Lys(iPr).

5. A GnRH antagonist according to claim 1 wherein Xaa.sub.5 is 4Aph(L- or D-Hor) and Xaa.sub.6 is D-4Aph(Ac), D-4Aph(atz), or D-3Pal.

6. A GnRH antagonist according to claim 1 wherein Xaa.sub.5 is 4Aph(L- or D-Hor), Q.sub.2 is Q and R is H or methyl.

7. A GnRH antagonist according to claim 1 wherein Xaa.sub.5 is 4Aph(L-

or D-Hor) and Xaa.sub.6 is D-Cit or D-Hci.

8. A GnRH antagonist according to claim 1 wherein Xaa.sub.6 is D-4Aph(D-Hor).

9. A GnRH antagonist peptide according to claim 1 wherein: X is For,  
Ac,

Acr, Pn, By, Vl, Vac, Bz or Q; A is 4Cl or 4F; Xaa.sub.5 is 4Aph(Q.sub.1) or 4Amf(Q.sub.1) with Q.sub.1 being a D-isomer, an L-isomer, or a D/L-isomer mixture of either Hor or Imz; Xaa.sub.6 is D-4Aph(Q.sub.2), D-4Amf(Q.sub.2), D-Cit, D-Lys(Nic) or D-3Pal, with Q.sub.2 being For, Ac, Q or Q.sub.1; and Xaa.sub.8 is Lys(ipr).

10. A GnRH antagonist according to claim 9 wherein Q.sub.1 is L- or D-Hor and Xaa.sub.6 is D-4Amf(Q), with R being H or methyl.

11. A GnRH antagonist according to claim 9 wherein X is Ac or Q; R is H or methyl; Xaa.sub.6 is D-4Aph(Q.sub.2), D-4Amf(Q.sub.2) or D-3Pal,  
with  
Q.sub.2 being Ac, Q or Q.sub.1.

12. A GnRH antagonist according to claim 1 having the formula:  
Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(L-Hor)-Xaa.sub.6-Leu-Lys(ipr)-Pro-Xaa.sub.10, wherein Xaa.sub.6 is D-4Aph(Ac), D-3Pal, D-4Aph(carbamoyl), D-4Amf(carbamoyl), D-4Amf(methylcarbamoyl) or D-4Aph(D-Hor).

13. A pharmaceutical composition for inhibiting the secretion of gonadotropins in mammals comprising, as an active ingredient, an effective amount of a GnRH antagonist according to claim 12 in association with a nontoxic diluent.

14. A method for inhibiting the secretion of gonadotropins in mammals comprising administering an amount of a pharmaceutical composition according to claim 13 which effects a substantial decrease in LH and  
FSH  
levels.

15. A method for in vivo or in vitro diagnosis of a condition where  
GnRH  
is causing excess hormonal secretion or tumor growth, which method comprises administering a GnRH antagonist peptide according to claim 12 and monitoring for hormonal secretion or for tumor cell proliferation.

16. A GnRH antagonist according to claim 1 having either the formula:  
Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(L-Hor)-D-4Aph(carbamoyl)-Leu-Lys(ipr)-Pro-D-Ala-ol; or the formula Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(L-Hor)-D-4Aph(carbamoyl)-Leu-Lys(ipr)-Pro-Ala-ol.

17. A GnRH antagonist according to claim 1 having either the formula:  
Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(L-Hor)-D-4Amf(carbamoyl)-Leu-Lys(ipr)-Pro-D-Ala-ol; or the formula:  
Ac-D-2Nal-D-4Cpa-D-3Pal-Ser-4Aph(L-Hor)-D-4Amf(carbamoyl)-Leu-Lys(ipr)-Pro-Ala-ol.

18. A GnRH antagonist peptide having the formula: X-D-2Nal-(A)D-Phe-D-Pal-Ser-(N.sup..alpha. Me)Xaa.sub.5-Xaa.sub.6-Leu-Xaa.sub.8-Pro-Xaa.sub.10 or a pharmaceutically acceptable salt thereof wherein:  
X

is an acyl group having not more than 7 carbon atoms or Q, with Q being ##STR13## and with R being H or lower alkyl; A is 4Cl, 4F, 4Br, 4NO.sub.2, 4CH.sub.3, 4OCH.sub.3, 3,4Cl.sub.2 or C.sup..alpha. Me4Cl; Xaa.sub.5 is 4Aph(Q.sub.1) or 4Amf(Q.sub.1) with Q.sub.1 being  
##STR14##

or a D/L mixture of either, Xaa.sub.6 is D-4Aph(Q.sub.2), D-4Amf(Q.sub.2), D-Lys(Nic), D-Cit, D-Hci or D-Pal, with Q.sub.2 being

For, Ac, 3-amino-1,2,4-triazole, Q or Q.sub.1 ; Xaa.sub.8 is Lys(ipr), Arg, Har, Arg(Et.sub.2) or Har(Et.sub.2); and Xaa.sub.10 is D-Ala-NH.sub.2, D-Ala-ol, Ala-ol, NHCH.sub.2 CH.sub.3, Gly-NH.sub.2, Ala-NH.sub.2, AzaGly-NH.sub.2, Agl-NH.sub.2, D-Agl-NH.sub.2, Agl(Me)-NH.sub.2 or D-Agl(Me)-NH.sub.2, provided however that when Xaa.sub.6 contains D- or L-Hor or D- or L-Imz or a D/L mixture of either, Xaa.sub.5 may have Ac, For or 3-amino-1,2,4-triazole as

Q.sub.1.

19. A GnRH antagonist peptide according to claim 18 wherein Q is carbamoyl or methylcarbamoyl; Q.sub.1 is L-Hor or D-Hor; and Xaa.sub.10 is D-Ala-NH.sub.2, D-Ala-ol or Ala-ol.

20. A GnRH antagonist peptide according to claim 18 wherein: X is For, Ac, Acr, Pn, By, Vl, Vac, Bz or Q; A is 4Cl or 4F; Xaa.sub.5 is Aph(Q.sub.1) or Amf(Q.sub.1) with Q.sub.1 being a D-isomer, an

L-isomer,

or a D/L-isomer mixture of either Hor or Imz; Xaa.sub.6 is D-Aph(Q.sub.2), D-Amf(Q.sub.2), D-Cit, D-Lys(Nic) or D-Pal, with

Q.sub.2

being For, Ac, Q or Q.sub.1 ; and Xaa.sub.8 is Lys(ipr).

=> d 1 bib

L20 ANSWER 1 OF 7 USPATFULL DUPLICATE 1  
AN 2001:14464 USPATFULL  
TI Pharmaceutical formulations for sustained drug delivery  
IN Gefter, Malcolm L., Lincoln, MA, United States  
Barker, Nicholas, Southborough, MA, United States  
Musso, Gary, Hopkinton, MA, United States  
Molineaux, Christopher J., Brookline, MA, United States  
PA Praecis Pharmaceuticals, Inc., Cambridge, MA, United States (U.S.  
corporation)  
PI US 6180608 B1 20010130  
AI US 1997-988851 19971211 (8)  
RLI Continuation-in-part of Ser. No. US 1996-762747, filed on 11 Dec 1996,  
now patented, Pat. No. US 5968895  
DT Utility  
FS Granted  
EXNAM Primary Examiner: Cintins, Marianne M.; Assistant Examiner:  
Delacroix-Muirheid, C.  
LREP Lahive & Cockfield, LLP, DeConti, Jr., Giulio A., Laccotripe, Maria C.  
CLMN Number of Claims: 50  
ECL Exemplary Claim: 1  
DRWN 8 Drawing Figure(s); 5 Drawing Page(s)  
LN.CNT 1333  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.